Correspondence

Cox inhibitors and bone healing

Sir—We read with interest the editorial "Avoid cox inhibitors after skeletal surgery!" by Aspenberg (2002) and the correspondence "Cox inhibitors and bone healing" by Kjaersgaard-Anderson and Jensen (2003).

In these two papers, the authors tried to answer questions relating to the effect of NSAIDs on bone healing after posttraumatic fractures and aseptic loosening of arthroplasties.

While we think their efforts were admirable, the following comments seem appropriate.

1. We agree with the authors statement that NSAIDs significantly reduce pain after acute fractures and postoperatively because of their regional analgesic and anti-inflammatory action in addition to their analgesic effect on the central nervous system (Prados and Baylock 1991). Some evidence also suggests that when NSAIDs are used in combination with opioid analgesics, they can help to reduce the amount of opioids needed without affecting the degree of analgesia (Prados and Baylock 1991). However, this reduction in the amount of the opioid seems not to reduce the opioid-related side effects such as nausea or respiratory depression (Sevarino et al. 1992). Moreover, the use of NSAIDs is associated with considerable side effects, particularly those on the gastrointestinal (Roth 1987), and renal systems (Perazella and Buller 1993, O'Callaghan 1994).

2. Bone formation and healing after traumatic fracture are complex phenomena affected by systemic and local factors (Curylo and Lindsey 1994). The use of NSAIDs in orthopaedic practice has been under discussion in recent years. Altman et al. (1995) showed, in an animal model, their adverse effect on fracture healing. These findings accorded with other research in this field in vivo and on animals—i.e., by Butcher and March (1996), Dimar et al. (1996) and Keller (1996) and more recently by us (Giannoudis et al. 2000). Although most of these papers have been criticized for being poorly designed and lacking sufficient evidence to support their conclusions, they remain the strongest evidence to date of the potential, adverse effects of NSAIDs on bone formation and healing in clinical practice and many of these papers have been considered a cornerstone for further research in this field.

3. Recently, we published a comprehensive survey and update on the role of NSAIDs in orthopaedic practice (Ankarath et al. 2003). In this paper, we found that the exact mechanism that NSAIDs inhibit bone healing is still unclear. A current hypothesis suggests that prostaglandins (PGs) play a role in osteogenesis and differentiation (Flannagan and Chambers 992, Keller 1996, Raisz 1999). COX-2 isoform has been shown to be the rate-limiting step in this process. After a fracture, COX-2 expression is increased due to adverse osteogenic signals (Raisz 1999). Suppression of COX-2 isoform causes a relative reduction in osteoblastogenesis (Keller et al. 1993, Raisz 1999). COX-2 is also associated with a decrease in the expression of the two genes essential for osteoblastogenesis—i.e., *osterix* and *cbfal* (Ducy et al. 1997, Nakashima et al. 2002).

All the above studies support the views about the adverse effects of NSAIDs, including those of COX-2 inhibitors on bone healing.

4. A recent innovation in selective COX-2 inhibitors seems to be a breakthrough because of their anti-inflammatory, analgesic and antipyretic actions without the gastrointestinal side effects (Roth et al. 1993). However, insufficient data are available as yet as to whether they can entirely solve the problem of NSAID-induced renal toxicity or prevent possible osteoblastic inhibitory activity of NSAIDs. Well-conceived research in this field is still needed in support or against their use in clinical practice. Until then we recommend that, on the basis of the clinical evidence available at present, all types of NSAIDs are best avoided in

acute fractures and when a bone graft is contemplated.

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