Non-steroidal anti-inflammatory drugs after hip replacement

Inhibit ectopic bone growth but do not reduce pain or disability

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The risks of cardiovascular and cerebrovascular toxicity associated with non-steroidal anti-inflammatory drugs (NSAIDs)^{1 2} have prompted reappraisal of the use of these drugs and led to the inclusion of "black box" warnings in related prescribing information in the United States.³ The European Medicines Agency may also extend its warnings, given that the Medicines and Healthcare Products Regulatory Agency is considering unpublished data from a new clinical trial⁴ along with all other evidence and is seeking expert advice this month from the Commission on Human Medicines (MHRA, personal communication, 2006).

Clinicians now avoid the use of NSAIDs in patients with established atheromatous disease. In this week's *BMJ*, however, Fransen and colleagues remind us that this class of drugs has many potential uses including inhibition of ectopic bone formation after joint replacement and postoperative pain relief.⁵ The authors report a randomised placebo controlled trial of a modest two week dose of postoperative ibuprofen (1200 mg a day) on pain and disability from ectopic bone formation a median of eight months after hip replacement. The trial found no effect of NSAIDs on pain and disability.

This work is interesting for three reasons. Firstly, this is a large and largely well conducted study concerning the most common and effective intervention for end stage hip disease—joint replacement. Secondly, it is important to publish such a relevant negative study, because publication biases undermine scientific progress and limit the usefulness of systematic reviews.⁶ Finally, even though the primary outcome was negative, the study was useful because it showed that ibuprofen reduced the risk of forming ectopic bone by 31% (95% confidence interval 56% to 83%), and that the effect increased with increasing degrees of ectopic ossification. Most would regard this as clinically relevant only if clinical outcomes (pain and function) were influenced, which they were not. So, was the difference in bone formation real and, if it was, why did the effect of treatment on ectopic ossification not reduce pain and disability?

The effect of NSAIDs on bone formation was probably real. This effect has already been established by a Cochrane review,⁷ and Fransen and colleagues' study in 20 centres with 900 patients is large enough to have generalisability across Australasia and perhaps

more widely. Nevertheless, these results showing no clinical benefit from lowering the risk of ectopic bone formation serve to remind us that guidelines in routine care should be based on clinically important outcomes, not unproved surrogate outcomes.⁸

Previous evidence suggests that cyclo-oxygenase-2 (COX 2) inhibitors might be more effective in inhibiting ectopic bone formation,⁹ provide good postoperative pain relief, and cause less bleeding than non-selective inhibitors. They might be an attractive alternative to NSAIDs, but this remains to be confirmed in a randomised controlled trial. And, importantly, treatment with selective or non-selective COX 2 inhibitors after joint replacement may compromise integration of the implant into the host bone bed, increasing the risk of late loosening of the implant and the need for repeated surgery.¹⁰ While this potentially important adverse effect is being explored in laboratory, clinical, and registry studies, it seems prudent to exercise caution in using COX 2 inhibitors after joint replacement.

The study by Fransen and colleagues has some limitations. The heterogeneous inclusion criteria impede direct comparison with other trials, and the lack of analysis of clinical subgroups bars exploration of the types of patients who might respond best to treatment. This study cannot answer questions about whether a longer course, a different NSAID, or more prolonged follow-up might yield clinical differences between treatment and placebo groups. Moreover, the authors did not discuss whether the outcome measures were sufficiently discriminating to detect differences,¹¹ especially when missing data were imputed by carrying the baseline observation forward and when there may have been a measurement artefact such as a floor effect in the main outcome measures.

There will never be a perfect clinical trial, however. The challenge for doctors lies in interpreting the relevance of such evidence to clinical practice. In this study by Fransen and colleagues the increase in major bleeding events in the patients who took NSAIDs, while numerically small, is statistically significant and reminds us that bleeds remain an important cause of morbidity and mortality with this class of drugs.¹² The frequency of bleeding events would almost certainly be increased by the use of higher doses and more prolonged administration of NSAIDs; hence further studies to test these interventions could be too risky.

On balance, this study shows that NSAIDs should not be given routinely after hip replacement surgery, but they might be used cautiously after due consideration of the overall likely benefits and risks to the patient.

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Ageism in services for transient ischaemic attack and stroke

Could be cut by emulating successful efforts against ageism in heart disease care

Societies based on market driven economies have deeply embedded value systems that inherently favour economically productive younger citizens and marginalise non-productive older citizens. Health services reflect the societies they serve. One manifestation of institutionalised ageism is overt and covert rationing of health care that discriminates against older people. This might be acceptable if the clinical outcomes of treating older people were inferior. However, the notion of age based rationing of treatment has become unsustainable and unethical as robust evidence has accumulated that shows comparable outcomes for treatment of older and younger people.

In England, decades of health service underfunding have provided an environment in which ageism has flourished—it is endemic.¹ Whenever a clinical stone is turned over, ageism is revealed—for example, in cancer services,² coronary care units,³ prevention of vascular disease,⁴ and in mental health services.⁵ To this list we must now add the management of transient ischaemic attacks and minor strokes, as a study in this week's *BMJ* by Fairhead and Rothwell shows.⁶

Fairhead and Rothwell investigated the management of transient ischaemic attacks and minor stroke in routine clinical services compared with a nested population receiving care based on national clinical practice guidelines.⁶ In the routine service they found substantial under-referral for carotid artery imaging and subsequent undertreatment of symptomatic

carotid artery stenosis in patients over the age of 80. The two study populations were comparable in terms of age, sex, and socioeconomic status and, for patients under 80, similar rates of performing clinical investigations were seen. Avoiding a disabling stroke is a priority in all patients, irrespective of age, and the authors conclude that the older patients in the population given routine care were discriminated against.

This study lacked, however, a view from the practitioners who invisibly contributed by providing care for these patients. Did they really make inconsistent clinical choices biased by the patients' ages? One qualitative study of the management of cardiovascular disease that identified ageism as a factor in suboptimal care for older people showed that doctors felt uncertain about the best and safest clinical practice, were unaware of the latest relevant research evidence, and were hampered by problems with local services.⁷

From an older person's perspective this apparently benign form of age discrimination is just as damaging as blatant ageism because older patients are still denied potentially beneficial treatments openly available to younger people. But understanding the reasons for such discrimination does suggest a role for education as an important corrective.

At the heart of the educational argument for stroke lies the counterintuitive notion that carotid endarterectomy for symptomatic carotid artery stenosis confers

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