

Interaction with NSAIDs

An observational study has suggested that regular use of NSAIDs (for more than 60 days per year) may abolish the cardioprotective effects of low-dose aspirin (1). A second observational study found that, among 7107 individuals discharged from hospital with diagnosed cardiovascular disease and prescribed low-dose aspirin (<325mg/day), regular use of ibuprofen was associated with an increased risk of death compared with use of aspirin alone (2). Other NSAIDs, including diclofenac, were not associated with an increased risk.

On the basis of a laboratory study (3), it has been suggested that ibuprofen may compete with aspirin for its binding site on the enzyme cyclo-oxygenase 1 (COX-1) enzyme. Aspirin binds irreversibly to this site whereas ibuprofen does not. Aspirin is rapidly metabolised so there is a relatively small period when it binds to the enzyme. If ibuprofen is present during this period, it may interfere with aspirin binding and therefore reduce the suppression of platelet function.

Although these data appear to support an interaction between aspirin and ibuprofen, the balance of evidence suggests that the outcome is not clinically significant (4). These reviewers therefore suggested that advice to avoid ibuprofen in patients taking low-dose aspirin for prevention of ischaemic heart disease is premature.

In a nested case-control study, 4,975 cases of acute myocardial infarction and death from ischaemic heart disease were matched with 20,000 controls and their use of NSAIDs was compared (5). The odds ratio (OR) for current NSAID use (including ibuprofen) compared with non-use was 1.07 (95% CI, 0.95 - 1.20). Similar results were found for the use of ibuprofen and aspirin at the same time compared with aspirin alone (OR 1.10, CI_{95%} 0.89 - 1.37). Treatment duration or daily dose did not change the results and there was no difference between individual NSAIDs. The reviewers therefore concluded that there was no clinically meaningful interaction between low-dose aspirin and NSAIDs, including ibuprofen.

Most recently, the European Medicines Agency has reviewed the cardiovascular safety of all non-COX selective NSAIDs such as ibuprofen (6). It found that the evidence from clinical trials is inadequate to assess a possible risk. Observational studies are, overall, inconclusive though an interaction between ibuprofen and aspirin cannot be ruled out. It does not mention data from spontaneous reports. A clinically important effect has not been clearly demonstrated.

The possibility of an interaction between naproxen and aspirin is also of concern. It has been suggested that naproxen itself may be cardioprotective, leading to its use in patients with arthritis and cardiovascular disease who need to take aspirin. A laboratory study has shown that naproxen reduces the inhibitory effects of aspirin on platelet function and COX-1 activity and this might reduce aspirin's cardioprotective effect (7). The interaction between these two agents is complex and more clinical trials are needed to establish the cardiovascular risks and benefits of available pain relievers.

The evidence regarding a clinically significant interaction between low-dose aspirin and ibuprofen (or other NSAIDs) is therefore inconclusive. However, it may be prudent for patients at high risk who take low-dose aspirin for cardioprotection to avoid the use of ibuprofen for chronic pain relief.

References:

1. Kurth T et al. Inhibition of clinical benefits of aspirin on first myocardial infarction by nonsteroidal anti-inflammatory drugs. *Circulation* 2003;108:1191-1195
2. MacDonald TM, Wei L. Effect of ibuprofen on cardioprotective effect of aspirin. *Lancet* 2003;361:573-574
3. Catella-Lawson F et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001;345:1809-1817
4. Cheema AA. Should people on aspirin avoid Ibuprofen? A review of the literature. *Cardiol Rev.* 2004 May-Jun;12(3):174-176
5. Garcia Rodriguez LA et al. Nonsteroidal antiinflammatory drugs and the risk of myocardial infarction in the general population. *Circulation.* 2004 Jun 22;109(24):3000-3006
6. Medicines and Healthcare Products Regulatory Agency. Cardiovascular safety of non-steroidal anti-inflammatory drugs. Overview of key data. (www.mhra.gov.uk/news/nsaidsbriefingdoc020805.pdf; accessed 3.8.05)
7. Capone ML et al. Pharmacodynamic interaction of naproxen with low-dose aspirin in healthy subjects. *J Am Coll Cardiol* 2005;45:1295-1301.

Updated November 2005