



Non-steroidal anti-inflammatory drugs and cardiovascular risk

To the Editor: Chin and Commerford¹ suggest the imbalance between eicosanoids (prostacyclins and thromboxanes) as a possible cause for the observed increase in cardiovascular risk with the cyclo-oxygenase-2 (COX-2) inhibitors and traditional non-steroidal anti-inflammatory drugs (NSAIDs).¹ I would like to suggest that the drug-drug interaction between the traditional NSAIDs and aspirin in post-myocardial infarction (MI) patients may be another contributing mechanism.

In people who have already had an MI, aspirin is well known to reduce cardiovascular risk, by reducing the risk of further acute MI or sudden death by 25%.² It is quickly absorbed from the stomach and upper small bowel, with a peak level about 30 minutes after ingestion. It has a short half-life (15 - 20 minutes), being rapidly cleared by the liver.

Despite its short half-life, aspirin is able to have a profound clinical effect because it binds irreversibly to the COX enzymes of platelets. This antiplatelet effect lasts the lifespan of the platelet. This action on the platelet is particularly important in the portal system, where the concentration of aspirin is highest. Low-dose aspirin preferentially inhibits the COX-1 enzymes, compared with high-dose aspirin which inhibits both COX-1 and COX-2 enzymes.³

Most traditional NSAIDs also bind to the COX-1 enzyme on the platelets at the same site as aspirin, but in a reversible fashion. Therefore co-administration of NSAIDs and aspirin in the post-MI patient may prevent the binding of aspirin to the COX-1 enzyme. After the NSAIDs have disassociated from the platelet COX-1 enzyme, the platelet is 'free' to function as normal without the beneficial 'anti-platelet effect' of aspirin. This effect was shown in normal subjects, where single-dose ibuprofen was administered 2 hours before aspirin. It was noted that the inhibition of platelet aggregation that is normally found with aspirin use was antagonised. This effect was also noted with multiple daily doses of ibuprofen, but not when aspirin ingestion preceded a single dose of ibuprofen.⁴ (Interestingly in this study, diclofenac was not shown to affect the pharmacodynamics of aspirin.)

This NSAID-aspirin drug interaction could be another mechanism to explain the observed increase in mortality in post-MI patients in the Danish registry study quoted by Chin and Commerford.⁵

Other studies have also suggested an increase in mortality when ibuprofen was used concomitantly with aspirin for secondary prevention of cardiovascular disease.⁶ This led MacDonald and Wei in their review to recommend avoiding chronic ibuprofen use at the same time as using aspirin for cardiovascular protection, especially if cardiovascular risk is high.⁷ While it is unclear whether the other NSAIDs have the same effect, MacDonald and Wei suggest that diclofenac at least may have a lesser effect.

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Dr Chin replies: The pharmacodynamic interaction between the NSAIDs and aspirin is poorly understood. In the study by Catella-Lawson *et al.*,¹ the concomitant administration of ibuprofen but not rofecoxib, paracetamol or diclofenac antagonised the irreversible platelet inhibition induced by aspirin. Thus, in the limited evidence available, treatment with ibuprofen has been shown in an experimental trial to limit the cardioprotective effects of aspirin in patients with increased cardiovascular risk.¹ Currently the US Food and Drug Administration recommends that ibuprofen be given at least 30 minutes after aspirin or at least 8 hours before aspirin to limit this interaction.² No data exist for definitive conclusions to be drawn about the interactions between celecoxib, indomethacin, other traditional NSAIDs and aspirin. Clearly the mechanism of cardiovascular hazard and the use of NSAIDs is complex. Although limited trial evidence suggests that the pharmacodynamic interaction between aspirin and NSAIDs may be a potential mechanism, a substantial body of evidence indicates that suppression of COX-2-dependent prostacyclin formation initiates and accelerates atherogenesis.³

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