EMA review of cardiovascular risks of NSAIDs: higher risk with diclofenac compared with ibuprofen/naproxen confirmed

In October 2012, a European Medicines Agency review on the cardiovascular safety of NSAIDs confirmed previous findings that diclofenac is associated with cardiovascular risks that are higher than ibuprofen and naproxen, and similar to the COX-2 inhibitors. Naproxen and low-dose ibuprofen are still considered to have the most favourable cardiovascular safety profiles of all non-selective NSAIDs. NSAIDs should be used at the lowest effective dose for the shortest time necessary to control symptoms, taking into account the patient’s individual risk factors.

Overview and current advice

In 2005, the Committee for Medicinal Products for Human Use (CHMP) identified an increased risk of thrombotic events, such as heart attack and stroke with COX-2 inhibitors. In 2006, they also concluded that a small increased risk of thrombotic events could not be excluded with non-selective NSAIDs, particularly when they are used at high doses for long-term treatment.

The CHMP advised that, although the benefits of NSAIDs outweighed the risks, these medicines should be used at the lowest effective dose for the shortest possible treatment duration. Prescribing should be based on the safety profiles of individual NSAIDs or COX-2 inhibitors and on individual patient risk profiles (e.g. gastrointestinal and cardiovascular). Prescribers should not switch between NSAIDs without careful consideration of the overall safety profile of the products and the patient’s individual risk factors, as well as their preferences.

QIPP Key therapeutic topics – Medicines management options for local implementation advises prescribers and prescribing managers to review the appropriateness of NSAID prescribing widely and on a routine basis, especially in people who are at higher risk of both gastrointestinal and cardiovascular morbidity and mortality (e.g. older patients). If an NSAID is obligatory, ibuprofen (1200 mg per day or less) or naproxen (1000 mg per day or less) should be considered first-line.

NICE guidance recommends that a proton pump inhibitor is co-prescribed with NSAIDs for people with osteoarthritis, rheumatoid arthritis, or low back pain (for people over 45 years).
New evidence

At the request of theMHRA, the CHMP has reviewed all the newly available evidence since its previous conclusions in 2006 in order to provide an updated opinion on the evidence of cardiovascular risk with non-selective NSAIDs

There were important limitations in all the recently available data due to the methodologies used and the populations studied. Nevertheless, for diclofenac the CHMP concluded that the latest study results were in line with previous evidence of an increased risk of heart attack, stroke or other thrombotic events. The currently available data consistently indicated that the risk is higher for diclofenac than other widely used non-selective NSAIDs, and is comparable to the risk seen with selective COX-2 inhibitors. Diclofenac will now be considered by the European Medicine Agency’s Pharmacovigilance Risk Assessment Committee.

For naproxen and ibuprofen, the CHMP concluded that the latest available evidence on cardiovascular risk was in line with the CHMP’s previous conclusions. The possibility of a small increased risk of thrombotic events cannot be excluded, particularly when these medicines are used at high doses and for long-term treatment.

A summary of the available information on the cardiovascular safety of COX-2 inhibitors and non-selective NSAIDs is available on the MHRA website.

Commentary

Commentary provided by Narinder Bhatta, (MSc; BSc (Hons), Consultant Pharmacist – Medication Safety, Cambridge University Hospitals NHS Foundation Trust

As the MHRA points out in a recent Drug Safety Update, the findings highlighted in this new 2012 review are not new; an increase in risk of heart attack and stroke with some non-selective NSAIDs, such as diclofenac, particularly with long-term use of high doses and in patients who are already at high risk, is well recognised. The 2006 review by the CHMP concluded that the thrombotic risk profile of diclofenac was similar to etoricoxib and possibly other COX-2 inhibitors. In the same year, a meta-analysis estimated that COX-2 inhibitors are associated with about three additional thrombotic events per 1000 patients per year in the general population. The MHRA reported that studies since 2006 have found an increased risk of cardiovascular events in all NSAID users not just those with baseline cardiovascular risk factors.

Following the previous advice from the CHMP and MHRA, there has been a significant shift in the prescribing of diclofenac to naproxen over the last few years, with an acceleration of change in prescribing since April 2011. (See Figure 1). However, in the quarter April to June 2012, diclofenac accounted for almost 800,000 prescription items (21% of all NSAID items) in primary care in England, and whilst the prescribing mean has moved there remains a wide variation between localities in the proportion of NSAIDs prescribed which are ibuprofen or naproxen.

Continuing efforts would seem to still be required, at least in some localities, to disseminate and implement this evidence - first widely communicated to UK prescribers by the MHRA in 2006.
Figure 1. NHS Prescription Services prescribing charts and data. NSAIDs: Ibuprofen & naproxen as a percentage of all NSAID items (PCT prescribing trend comparison, England)

References

1. EMA. European Medicines Agency concludes action on COX-2 inhibitors, June 2005
2. EMA. European Medicines Agency review concludes positive benefit-risk balance for non-selective NSAIDs. October 2006
4. NPC. Key therapeutic topics—Medicines management options for local implementation. Version 4.2, April 2012
8. EMA. Questions and answers on the review of non-selective non-steroidal anti-inflammatory drugs (NSAIDs) and cardiovascular risk. October 2012
9. MHRA. NSAIDs: further evidence that the cardiovascular risk with diclofenac is higher than other non-selective NSAIDs and similar to the selective COX-2 inhibitors. Drug Safety Update. October 2012, vol 6, issue 3, S1
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