Non-steroidal anti-inflammatory drugs: new information and warnings about cardiovascular risk

A meta-analysis notes that COX-2 inhibitors and diclofenac are associated with increased incidence of major vascular events.

Overview: An increased risk of heart attack and stroke with some non-selective non-steroidal anti-inflammatory drugs (NSAIDs), such as diclofenac, is well recognised, particularly with long-term use of high doses and in patients who are already at high risk. Warnings for healthcare professionals and patients are included in the summaries of product characteristics and in the British national formulary.

See the Medicines and Healthcare Products Regulatory Agency’s (MHRA) webpage on cardiovascular safety of COX-2 inhibitors and non-selective NSAIDs for more information.

Current advice: The European Medicines Agency’s Pharmacovigilance Risk Assessment Committee has recommended updates to its treatment advice for diclofenac in light of the findings of a Europe-wide review of the cardiovascular safety of NSAIDs. The review found further evidence that the cardiovascular risk of diclofenac is similar to that of COX-2 inhibitors.

The June 2013 edition of the MHRA’s Drug Safety Update advised that, consistent with COX-2 inhibitors, systemic diclofenac is now contraindicated in people with established ischaemic heart disease, peripheral arterial disease, cerebrovascular disease, or congestive heart failure (New York Heart Association classification II–IV). Patients with these conditions should be switched to an alternative treatment at their next routine appointment.

Diclofenac treatment should be initiated only after careful consideration in people with significant risk factors for cardiovascular events (for example, hypertension, hyperlipidaemia, diabetes mellitus, or smoking). The new advice applies to all systemic formulations including those available over the counter in pharmacies; it does not apply to topical formulations.

New evidence: A meta-analysis by the Coxib and traditional NSAID Trialists’ Collaboration (2013) aimed to quantify the cardiovascular and gastrointestinal risks of NSAIDs using data from randomised controlled trials. It included 280 trials (n=124,513) of an NSAID compared with placebo and 474 trials (n=229,296) of an NSAID compared with another NSAID. The primary outcomes were major vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death) and upper gastrointestinal complications (perforation, obstruction, or bleed).

Compared with placebo, major vascular events were significantly increased by more than a third for COX-2 inhibitors (rate ratio=1.37, 95% confidence interval [CI] 1.14 to 1.66, p=0.0009) and diclofenac 150 mg daily (rate ratio=1.41, 95% CI 1.12 to 1.78, p=0.0036). This was mainly due to an increase in major coronary events (non-fatal myocardial infarction or death from coronary heart disease). The absolute increase in risk was small but serious: compared with placebo, COX-2 inhibitors or
diclofenac 150 mg daily caused around 3 additional major vascular events per 1000 participants per year, 1 of which was fatal.

Ibuprofen 2400 mg daily did not significantly increase the risk of major vascular events compared with placebo; however, it doubled the risk of major coronary events (rate ratio=2.22, 95% CI 1.10 to 4.48, p=0.0253). Naproxen 1000 mg daily did not significantly increase major vascular or coronary events compared with placebo. The proportional cardiovascular and gastrointestinal risks of all NSAIDs appeared independent of baseline characteristics, including vascular risk.

The risk of hospitalisation due to heart failure was approximately doubled by all NSAIDs studied, compared with placebo. In addition, COX-2 inhibitors and diclofenac doubled the risk of upper gastrointestinal complications (mainly bleeds), and ibuprofen and naproxen quadrupled the risk, compared with placebo.

**Commentary:** “The new meta-analysis and subsequent MHRA alert reinforce all previous information about the cardiovascular and gastrointestinal risks of NSAIDs and provide additional support to existing guidance.

“The **MHRA advises** that the decision to prescribe an NSAID should be based on an assessment of a person's individual risk factors, including any history of cardiovascular and gastrointestinal illness. Naproxen and low-dose ibuprofen (1200 mg per day or less) are considered to have the most favourable thrombotic cardiovascular safety profiles of all non-selective NSAIDs. The lowest effective dose should be used for the shortest duration necessary to control symptoms. However, a cohort study in people who had had a myocardial infarction suggests that even short-term use of NSAIDs (some for as little as 1 week) is associated with an increased risk of death or recurrent myocardial infarction.

"As described in the QIPP key therapeutic topic on NSAIDs, the volume of NSAID prescribing is decreasing nationally, and there has also been a significant shift in the prescribing of diclofenac to naproxen since April 2008. However, diclofenac still accounts for approximately 700,000 prescription items (18% of all NSAIDs) per quarter in primary care in England, and the proportion of NSAIDs prescribed that are ibuprofen or naproxen ranges from 51.5% to 78.8% across primary care trusts.

"The challenge for clinicians therefore, is to ensure that use of all NSAIDs, of all durations, is reviewed in all settings. In secondary care this means using alternatives to diclofenac for acute treatment in emergency departments and for day surgery, as well as chronic treatment for example rheumatological conditions. In primary care, patients should be systematically reviewed starting with those at higher risk of both gastrointestinal and cardiovascular morbidity and mortality (for example, older people).” – **Narinder Bhalla, Consultant Pharmacist, Medication Safety, Cambridge University Hospitals NHS Foundation Trust**

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