Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

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NSAIDs and risk of acute myocardial infarction

An analysis that used pooled individual patient data found taking any NSAID was associated with an increased risk of acute myocardial infarction (AMI). The results showed these increased risks with all five NSAIDs studied, including naproxen, and in both short-term use (less than a week) and longer term use. This study reinforces NICE guidance to avoid NSAIDs if possible, especially in those at high risk of having a cardiovascular disease (CVD) event. If an NSAID is required, the lowest effective dose should be used for the shortest duration necessary to control symptoms, and the need for symptomatic relief and treatment response should be reviewed regularly. The results suggest that similar cautions should apply to over the counter use.

Reference: Bally M, Dendukuri N, Rich B, et al. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. BMJ. 2017;357:j1909.

What do we know already?

- Clinical trial and observational evidence suggests that both traditional non-steroidal anti-inflammatory drugs (NSAIDs) and selective cyclo-oxygenase-2 (COX-2) inhibitors can increase the risk of coronary heart disease and stroke.
- The MHRA advise that selective COX-2 inhibitors have higher CVD risk than most other NSAIDs. Diclofenac has a similar high risk to these and should no longer be prescribed to those at high CVD risk. Naproxen and low-dose ibuprofen (≤1200 mg/day) are considered to have the most favourable CVD safety profiles of all non-selective NSAIDs.
- The decision to prescribe an NSAID should be based on an assessment of a patient's individual risk factors, including any history of cardiovascular, renal and gastrointestinal illness.
- The MHRA state that the lowest effective dose should be used for the shortest duration necessary to control symptoms. A patient's need for symptomatic relief and response to treatment should be re-evaluated periodically.

What does this evidence add?

- Few prospective clinical trials have provided evidence on the risk of AMI as this is a relatively rare adverse event over the duration of these studies, and subjects with high CVD risk tend to be excluded from such research. The authors of this new study claim that the timing of AMI risk, the effect of dose, treatment duration, and the comparative risks between NSAIDs have been poorly understood.
- The study specifically looked at the use of diclofenac, ibuprofen, naproxen, celecoxib and rofecoxib* in clinical practice (not in clinical trial settings). Using a Bayesian meta-analysis of individual patient data the research suggests that all these drugs, including naproxen, appear to be associated with an increased risk of AMI.
  [*Rofecoxib is a drug that was withdrawn from the market in 2004].
- Unlike other studies where higher CVD risk was seen with COX-2 inhibitors, the risk of AMI with celecoxib did not seem to be greater than with traditional NSAIDs.
- The risk in this study appeared to happen early in use; onset of increased risk occurred within the first week. It continued up to 30 days, and beyond, but the size of risk did not increase further after the first 30 days.
- There was evidence that higher doses were associated with higher risk even if used for less than one week.
- The main criticism of these findings is that they are subject to confounding as it may be that the presence of pain, rather than the use of a pain relieving drug (NSAID), may be the factor associated with AMI. A further criticism is that the study did not look at AMI events relative to other risk factors for CVD, although it did try to correct for them as confounding factors.

- Alongside MHRA guidance and gastrointestinal and renal concerns, this study reinforces the need for particular caution in prescribing NSAIDs to any person with relatively high risks of CVD. Ideally they should not be prescribed to anyone with a history of coronary heart disease, heart failure or stroke. Also, greater care is needed in people with hypertension, those with high CVD risk (for example, greater than10% 10-year risk using QRISK2), and in those with diabetes. This study suggests that this increased caution may also apply in the context of short-term 'over the counter' NSAID use.

Study details

Participants:

- Studies were identified which looked at computerised drug prescription or medical databases, in the general or an elderly population and documented acute myocardial infarction as specific outcome, and also recorded use of selective COX-2 inhibitors and traditional NSAIDs.
- After searching, 82 studies were initially identified. 67 were excluded as they did not fulfil selection criteria. Of the remaining 15, seven did not allow suitable analysis, and four were excluded as individual patient data was not made available. This left four studies for pooling of data. Two were from Canada, one from Finland and one from the UK.
- From these four studies, an individual patient data meta-analysis, involving a cohort of 446,763 individuals including 61,460 with AMI was conducted. The method used was said to enable emulation of a large, pragmatic randomised trial.

Intervention and comparison:

- The study compared risk of AMI in NSAID users with non-users, allowed for time dependent analyses, and took steps to minimise effects of confounding and misclassification bias.
- Drug exposure was modelled as an indicator variable incorporating the specific NSAID, when it was used, duration of use, and dose.
- A Bayesian analysis was performed combining prior information to yield a posterior probability distribution for each parameter of interest.
- The outcome measured was the summary adjusted odds ratio of first acute myocardial infarction after study entry for each category of NSAID use at index date (date of AMI for cases, matched date for controls) versus non-use in the preceding year and the posterior probability of AMI.

Outcomes and results:

- All NSAIDs, including naproxen, were associated with an increased risk of acute myocardial infarction. The overall increased risk with celecoxib did not reach statistical significance except with the low dose (≤ 200mg/day) subset.
- Taking any dose of any NSAID for one week, one month, or more than a month was associated with an increased risk of myocardial infarction.
- With use for longer than one month, risks did not appear to exceed those associated with shorter durations.
- With use for one to seven days at any dose the probability of increased myocardial infarction risk (posterior probability of odds ratio >1.0) was:
  - **Diclofenac** – a 50% increased risk (adjusted odds ratio [OR] 1.50, 95% credible interval* [CrI] 1.06 to 2.04). Probability of increased AMI risk (posterior probability of OR>1.0) was 99%.
  - **Ibuprofen** – a 48% increased risk (adjusted OR 1.48, 95% CrI 1.00 to 2.26]. Probability of increased AMI risk was 97%.
  - **Naproxen** – a 53% increased risk (adjusted OR 1.53, 95% CrI 1.07 to 2.33). Probability of increased AMI risk was 99%.
  - **Rofecoxib** – a 58% increased risk (adjusted OR 1.58, 95% CrI 1.07 to 2.17). Probability of increased AMI risk was 99%.
  - **Celecoxib** – a 24% increased risk (adjusted odds ratio 1.24, 95% CrI 0.91-1.82: *not statistically significant*) Probability of increased AMI risk was 92%.
- Greater risk of AMI was associated with higher dose of NSAIDs; use for 8-30 days at a high daily dose (diclofenac >100 mg, ibuprofen >1200 mg, and naproxen >750 mg) was associated with the greatest harms.

Credible intervals are similar to* confidence intervals*, but are generated by Bayesian analysis.

Level of evidence: Level 1 (good quality patient-oriented evidence) according to the **SORT criteria.**
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