Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

Published: November 2014

Non-steroidal anti-inflammatory drugs and risk of venous thromboembolism

A systematic review and meta-analysis of observational studies found that there was a statistically significantly increased risk of venous thromboembolism (VTE) among users of non-steroidal anti-inflammatory drugs (NSAIDs) compared to non-users of NSAIDs (pooled risk ratio 1.80; 95% CI 1.28 to 2.52). However, the meta-analysis has a number of important limitations and these results should be interpreted with caution. The decision to prescribe an NSAID should continue to be based on an assessment of a person's individual risk factors, including any history of cardiovascular and gastrointestinal illness. Where an NSAID is needed, the lowest effective dose should be prescribed for the shortest period of time to control symptoms and the need for long-term treatment should be reviewed periodically.

Overview and current advice:

Non-steroidal anti-inflammatory drugs (NSAIDs) have analgesic and anti-inflammatory properties and can be used for many painful conditions. There are long-standing and well-recognised gastrointestinal and renal safety concerns with all NSAIDs. There is also substantial evidence confirming an increased risk of cardiovascular events with many NSAIDs, including COX-2 selective inhibitors and some traditional NSAIDs such as diclofenac. The Medicines and Healthcare products Regulatory Agency (MHRA) has previously issued safety advice on the use of non-selective NSAIDs and COX-2 selective inhibitors and their association with cardiovascular events. This can be summarised as follows:

- All NSAID use (including COX-2 selective inhibitors) can, to varying degrees, be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of baseline cardiovascular risk factors or duration of NSAID use; however, the greatest risk may be in those receiving high doses long-term.
- COX-2 selective inhibitors, diclofenac (150 mg daily) and ibuprofen (2.4 g daily) are associated with an increased risk of thrombotic events. The increased risk for diclofenac is similar to that of licensed doses of etoricoxib. Naproxen (1 g daily) is associated with a lower thrombotic risk, and low doses of ibuprofen (1.2 g daily or less) have not been associated with an increased risk of myocardial infarction.
- The lowest effective dose of NSAID should be prescribed for the shortest period of time to control symptoms and the need for long-term treatment should be reviewed periodically.
New evidence

Since arterial and venous thrombosis share several pathophysiological mechanisms, there is a concern that NSAIDs may also increase the risk of venous thromboembolism (VTE). A systematic review and meta-analysis of published studies has examined the association between NSAID use and the risk of VTE (Ungprasert et al. 2014)\(^1\). Six observational studies were identified for inclusion: 5 case-control studies (carried out in Europe) and 1 cohort study (carried out in USA). One study included patients with pulmonary embolism only, while the other studies included patients with deep vein thrombosis or pulmonary embolism. The authors were unable to use data from randomised controlled trials (RCTs) in this meta-analysis because VTE is a less common adverse effect that requires a larger sample size and a longer duration of follow-up than those found in RCTs of NSAIDs.

There were 21,401 VTE events identified in the 6 studies. Pooled analysis of data from the 6 studies found a statistically significantly increased risk of VTE in people who used any NSAID compared with those who did not use an NSAID (pooled risk ratio 1.80; 95% confidence interval [CI] 1.28 to 2.52). The authors also reported a statistically significantly increased risk of VTE with the use of a COX-2 selective inhibitor from 3 studies (pooled risk ratio 1.99; 95% CI 1.44 to 2.75).

All NSAIDs were evaluated as a class in this meta-analysis, with COX-2 selective inhibitors reported as a sub-group. No information was reported on the type of NSAID used; the duration of use, dosage, indication, criteria for determining COX-2 selectivity or any other risk factors for VTE.

Commentary

These observational data suggest an association between NSAID use and increased VTE risk. However, this finding should be interpreted with caution.

This meta-analysis has a number of important limitations. Firstly, the included studies did not provide sufficient data to adjust for important potential confounders such as selection bias or an increased risk for VTE with one or more NSAIDs but not with others. Secondly, the results were highly heterogeneous with an I\(^2\) of 95%. The authors also reported the possibility of publication bias. Thirdly, most of the included studies were conducted using a medical registry-based database, an approach subject to coding inaccuracy. In addition the definition and method of verification for NSAID exposure varied between the studies; some studies used a pharmacy record database while others used a structured or phone interview.

The decision to prescribe an NSAID should continue to be based on MHRA advice which includes an assessment of a person’s individual risk factors, including any history of cardiovascular and gastrointestinal illness. More data are required to determine whether individual NSAIDs or NSAIDs as a class do or do not increase risks of VTE.

Study sponsorship

The authors report that no specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the systematic review and meta-analysis.
References


About this Medicines Evidence Commentary

Medicines Evidence Commentaries form part of NICE’s Medicines Awareness Service and help contextualise important new evidence, highlighting areas that could signal a change in clinical practice. They do not constitute formal NICE guidance. The opinions of contributors do not necessarily reflect the views of NICE.

Visit Evidence Search

Copyright © 2014 National Institute for Health and Care Excellence. All Rights Reserved.