Stroke risk and NSAIDs: a systematic review of observational studies

Varas-Lorenzo C, Riera-Guardia N, Calingaert B, Castellsague J, Pariente A, Scotti L, Sturkenboom M, Perez-Gutthann S

CRD summary

The review concluded there was a variable effect on the risk of ischaemic stroke across individual non-steroidal anti-inflammatory drugs (NSAIDs); rofecoxib and diclofenac were associated with an increased risk. The potential for missed studies and the small number of variable studies in each analysis mean the conclusions should be treated with caution.

Authors' objectives

To assess the risk of stroke associated with the use of individual non-steroidal anti-inflammatory drugs (NSAIDs).

Searching

PubMed was searched for English language articles from January 1990 to 2008; search terms were reported. Reference lists of relevant articles were scanned for additional articles.

Study selection

Observational cohort or case-control studies that reported the risk of cardiovascular events associated with individual NSAIDs compared to the non-use of NSAIDs were eligible for inclusion. Studies had to report measures of association that compared the risk of acute ischaemic and/or hemorrhagic stroke between intervention and control groups.

Studies were conducted in the Netherlands, Denmark and the UK between 1990 to 2004. Naproxen, ibuprofen, diclofenac, celecoxib and rofecoxib were the most frequently used treatment. The age of participants ranged from over 20 years to 99 years. Studies used diagnoses from out-patient and hospital. Most studies reported hemorrhagic stroke including or excluding subarachnoid haemorrhage, the remaining studies reported outcomes for ischaemic stroke. Studies included both new and prevalent users of NSAIDs. Some studies reported only the evaluation of incident events. Most studies collected data from hospital registries

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality

Study quality was assessed using the Newcastle-Ottawa Scale which included criteria on the selection of study groups, comparability between groups and ascertainment of the exposure in case-control studies or the outcome in cohort studies.

Two reviewers independently assessed study quality. Disagreements were resolved through consensus.

Data extraction

Data were extracted for acute ischaemic and/or hemorrhagic stroke from each study and used to calculate risk ratios (RRs) and corresponding 95% confidence intervals (CIs).

The authors did not state how many reviewers extracted data.

Methods of synthesis

Pooled risk ratios and 95% confidence intervals were estimated using a fixed-effect model and random-effects model. Heterogeneity was assessed by graphical inspection of forest plots and by Cochran's X^2 test, Tau^2 and the I^2 statistic. Sensitivity analyses were used to explore heterogeneity. Publication bias was assessed by visual inspection of funnel plots.

Results of the review

Six studies (1,341,673 participants) were included in the review; four cohort studies and two nested case-control studies. Sample sizes ranged from 7,636 to 469,647. Four studies scored maximum points for selection of studies. All studies scored maximum points for comparability and for ascertainment of outcome in cohort studies or exposure in

case-control studies.

There was an increase in all subtypes of incident stroke with use of rofecoxib (RR 1.64, 95% CI 1.15 to 2.33, four studies, I^2=74%), and diclofenac (RR 1.27, 95% CI 1.08 to 1.48, four studies, I^2=4%). There were no significant differences between intervention and control groups for naproxen, ibuprofen or celecoxib. There was an increased risk of ischaemic stroke with rofecoxib (RR 1.82, 95% CI 1.09 to 3.04, three studies, I^2=91%) and diclofenac (RR 1.20, 95% CI 0.99 to 1.45, four studies, I^2=33%). There were no significant differences reported between groups for naproxen and ibuprofen.

There was insufficient data to estimate the pooled risk rate by dose and duration and for other individual NSAIDs and non-ischaemic stroke subtypes, but details for individual studies were reported. Sensitivity analysis removing the study that reported high risk ratios for naproxen and rofecoxib was conducted but significant heterogeneity remained across studies. Removal of one study that included only men and reported current exposure differently to the other studies reduced heterogeneity, and the result for rofecoxib remained statistically significant.

There was some evidence of publication bias.

Authors' conclusions

The results from observational studies suggested a variability of effect on the risk of ischaemic stroke across individual NSAIDs; rofecoxib and diclofenac were associated with an increased risk compared with the non-use of NSAIDs.

CRD commentary

The review question was clear and inclusion criteria reported. Only one electronic database was searched and only studies in English were included which meant some studies may have been missed. Formal assessment found some evidence of publication bias. Study quality was assessed and results were reported. Only cohort studies and case-control studies were included which were study designs liable to multiple biases. Appropriate methods were used to reduce reviewer error and bias for assessment of study quality, but it was unclear whether similar methods were used for the selection of studies or the extraction of data. Studies were combined in a meta-analysis and sources of heterogeneity were explored. However, it should be considered that only a few studies were included in some analyses.

The potential for missed studies and the small number of variable studies in each analysis mean the conclusions should be treated with caution.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that further research was needed to evaluate individual NSAIDs, as well as the effect of dose and duration, concomitant use of aspirin and separately for each stroke subtype and to address the potential for residual confounding.

Funding

The European Community's Seventh Framework Programme: the SOS project.

Review authors declared several conflicts of interest relating to NSAID manufacturers.

Bibliographic details

Varas-Lorenzo C, Riera-Guardia N, Calingaert B, Castellsague J, Pariente A, Scotti L, Sturkenboom M, Perez-Gutthann S. Stroke risk and NSAIDs: a systematic review of observational studies. Pharmacoepidemiology and Drug Safety 2011; 20(12): 1225-1236

PubMedID

21971833

DOI

10.1002/pds.2227

Original Paper URL
http://onlinelibrary.wiley.com/doi/10.1002/pds.2227/abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Anti-Inflammatory Agents, Non-Steroidal /administration & dosage /adverse effects; Brain Ischemia /chemically induced /epidemiology /pathology; Dose-Response Relationship, Drug; Humans; Risk; Stroke /chemically induced /epidemiology /pathology; Time Factors

AccessionNumber
12011007448

Date bibliographic record published
08/03/2012

Date abstract record published
20/07/2012

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.