Nonsteroidal Anti-Inflammatory Drugs as Risk Factors for Spontaneous Intracerebral Hemorrhage and Aneurysmal Subarachnoid Hemorrhage

To the Editor:

I read with interest 2 recent Danish articles concerning nonsteroidal anti-inflammatory drugs (NSAIDs) as risk factors for intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH).1,2 The authors of the latter article seem to be more objective and to have written the article carefully, taking into account several sources of bias.2 However, the authors of both articles state that there has been published previously only 1 study on NSAIDs as a risk factor. The authors did not do their literature review carefully because they did not find that our study group had published in esteemed journals during the last decade several articles in which the use of NSAIDs (aspirin within 1 week or nonaspirin NSAIDs within 24 hours before hemorrhage) was analyzed as a risk factor for ICH and SAH as well as their role in outcome after these hemorrhages.3–10 Although our studies were done among patients of working age except for one,10 these were not subjected to such sources of bias as were the Danish studies. We also evaluated simultaneously the independent role of several well-known risk factors for hemorrhagic stroke subtypes. Our patient populations were population-based for ICH patients8 and hospital-based for SAH patients4; the latter included only cases with verified aneurysm ruptures but excluded those who died before hospital admission. In addition, we also used laboratory markers of alcohol consumption and aspirin use to improve reliability of the data and decrease possibility of recall bias.

In our data, 30% of SAH patients, 28% of ICH patients, and 20% of controls (patients with acute diseases without bleeding tendency) had used NSAIDs before hemorrhage or control disease.3–9 More than 70% of users of NSAIDs had used preparations containing aspirin that were mostly obtained without prescription by physician from the pharmacy (over-the-counter [OTC] use).4,6,10 Most SAH patients had used NSAIDs before bleeding because of premonitory warning symptoms or minor leaks. Univariate odds ratios (95% confidence intervals) of use of NSAIDs for ICH and SAH were 1.5 (0.92 to 2.3) and 1.7 (1.18 to 2.5), respectively, but multivariate odds ratios were clearly insignificant.4,6 Among the elderly, use of NSAIDs was more common.10 Independent risk factors for SAH were cigarette smoking, recent alcohol consumption, and possibly hypertension.4 Corresponding risk factors for ICH were hypertension, recent alcohol consumption, and anticoagulant treatment.6 None of these could be reliably evaluated in the present Danish studies.1,2 In addition, reliability of use of NSAIDs was limited.

Diagnoses obtained from hospital discharge registers or other official registers have not been shown to be reliable because these are filled out by persons with different kinds of expertise. Retrospective checking of hospital medical records for recording of risk factors and of use of medicines before the bleeding is also quite unreliable. Interview of patients and family members with a structured questionnaire soon after stroke with possible use of laboratory markers is much more reliable in this respect. Use of a pharmacoepidemiological database for NSAIDs use is also unreliable since the exact time of use of NSAIDs relative to bleeding is important to see whether NSAIDs even can cause bleeding. Furthermore, NSAIDs, particularly aspirin, are sold mostly as OTC medicine both in Finland and in Denmark. So, there remained considerable source of bias whether or not NSAIDs have been used shortly before hemorrhage. The method of recording data was also likely a reason for an observed low prevalence of NSAID use.

Similarly, the use of different medicines of prescription registry as proxy measures of diseases is unreliable. Compliance of use of prescribed medicines may be low and not necessarily similar in cases and controls. For hypertension, poor compliance of use of antihypertensives is a more important risk factor for ICH than use of antihypertensives.6,10 Almost half of hypertensive patients with ICH have not used antihypertensive mediation before hemorrhage because of either patient- or physician-related reasons.9 Similarly, risk associated with anticoagulant treatment is dependent on intensity of anticoagulation and not on treatment itself.6 In fact, the only reliable information is for diabetes mellitus, which seems to be a risk factor for ICH, as was also previously suggested.8

Use of aspirin might more likely cause an increased risk for ICH than nonaspirin NSAIDs because of a considerably longer time of effect of aspirin. It seems that high-dose aspirin may have increased risk for ICH only among elderly people.10 Although NSAIDs do not seem to significantly increase risk of either ICH or SAH or have an effect on outcome after ICH, aspirin taken before SAH (ie, also before knowledge of severity of bleeding) may improve outcome since use of aspirin before SAH can decrease risk for delayed ischemia and cerebral infarction.3,5 Thus, use of NSAIDs, particularly aspirin, should not be denied for patients with verified unruptured aneurysms.

Seppo Juvela, MD, PhD
Department of Neurosurgery
Helsinki University Central Hospital
Helsinki, Finland

Letters to the Editor

Response

We wish to thank Dr Juvela for drawing our attention to several studies from his group in which use of nonsteroidal anti-inflammatory drugs (NSAIDs) was reported in cases of intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH), including 2 case-control studies with hospital-based controls\(^1\)\(^–\)\(^3\) and a single case-control study with community-based controls.\(^4\) In all 3 of these studies a time window of drug use of 1 week prior to the index date (date of hospitalization for cases) was used and data on drug use were based on self-report. Only 1 of these 3 studies clearly distinguished between nonaspirin NSAIDs (NANSAIDs) and aspirin (ASA) in the presented analyses. In this study, which included 98 cases of ICH and 206 controls, the authors report results of a multivariate model for the odds ratio of ICH in NANSAID users (OR: 4.00; 95% CI: 1.02 to 15.6), when controlling for the effect of recent heavy drinking of alcohol, hypertension, ischemic stroke, epilepsy, physical exertion, age, sex, history of epistaxis, and the interaction between NANSAID use and epistaxis.\(^3\) A similar model including use of ASA (instead of NANSAID) resulted in an odds ratio of 16.9 (95% CI: 2.48 to 114). This result, along with the fact that the majority of NANSAID users concurrently used ASA mainly in high doses (>1225 mg/wk), led the researchers to conclude that the elevated risk associated with NANSAID use was primarily due to concurrent use of ASA. However, the odds ratio of ICH in users of NANSAIDs with no concurrent use of ASA was not reported. The cases were not first-ever cases of ICH (21% had suffered a previous ischemic stroke and 8% a previous hemorrhagic stroke). Factors influencing survival may therefore also be at play in these prevalent cases. Further, the way data were collected differed in cases and controls. Cases or their relatives (proportion of proxy interviews not reported) underwent face-to-face interviews. Controls were telephone-interviewed, and family members of controls were not interviewed. The small outcome misclassification and the differential exposure ascertainment are important methodological weaknesses and make the validity of this study questionable.

In his letter to the editor, Dr Juvela reports results of univariate analyses of NSAIDs for ICH (OR: 1.5 [0.92 to 2.3]);\(^2\) and SAH (OR: 1.7 [1.18 to 2.5]).\(^5\) The latter odds ratio was not reported in the article cited.\(^1\) We take note that Dr Juvela in his letter reports that most patients had used NSAIDs to treat premonitory warning symptoms or minor leaks. The increased odds ratios observed in these studies are therefore probably due to protopathic bias, a variant of confounding by indication (treatment of the initial symptoms of intracranial bleeding with pain killers), a finding that we were able to document in our study.\(^4\)

Dr Juvela raises several methodological issues concerning our study. We feel that most of his points have been adequately addressed in the discussion section of our article and that of our colleagues.\(^1\)\(^–\)\(^3\)\(^,\)\(^,\)\(^5\) We would, however, like to stress that NANSAIDs are mainly prescribed in Denmark. As already stated by our colleagues,\(^5\) the only NANSAID sold over-the-counter in Denmark is ibuprofen 200 mg (tablet formulation), which was cheaper if prescribed. We compared the prevalence of current use of NANSAIDs in the community controls where information on drug use was derived from a prescription register, with data on self-reported use of these drugs in a sample of 4441 Danish twins who underwent home-based in-person structured interviews conducted by trained interviewers. The prevalence of current NANSAID use (14-day time window) stratified by age and sex was highly comparable in the control and survey populations.\(^5\) We therefore conclude that the prescription register data adequately captured use of NANSAIDs in the Danish studies.\(^1\)\(^–\)\(^3\)\(^,\)\(^5\)


Response

We thank Dr Juvela for his interest in our study.\(^1\) The objective of our study was to examine the possible association between use of nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) and the risk of first-time intracerebral hemorrhage (ICH). Data on this issue have been sparse in the literature thus far and we were able to identify only 1 previous study at the time of our literature search.\(^2\) Although the studies by Dr Juvela and colleagues were interesting in many ways, we could not find any data on the risk of ICH associated with use of nonaspirin NSAIDs in these studies. Only 1 of these studies distinguished between aspirin and nonaspirin NSAID; however, 74% (38/52) of the cases who used nonaspirin NSAIDs in this study had concurrent use of aspirin.\(^3\) Risk estimates for nonaspirin NSAIDs adjusted for concurrent use of aspirin were not presented in the article.\(^3\)

Registry-based studies come with a number of strengths and limitations that should be recognized when interpreting the studies.\(^4\)\(^–\)\(^5\) The strengths include the possibility of a population-based study design, a large sample size, and prospectively collected data on exposures, outcomes, and confounders. In contrast, the fact that selection, quality, and methods of collection of registry data are not under the control of the researcher may hamper the registry-based studies. The potential implications of such limitations for the interpretation of the reported results of our study are discussed in details in our article.\(^1\)

Like the registry-based studies, studies based on primary data also have a number of strengths and limitations, eg, the presence of potential recall bias and statistical imprecision should be taken into account when interpreting the results of case-control studies based on retrospectively collected data with relatively small sample sizes like the studies by Dr Juvela et al.\(^3\)

In conclusion, no single study can be expected to provide a definitive answer to the question of whether use of nonaspirin NSAIDs increases the risk of ICH. Combining the available information from various study designs, taking into account the specific advantages and disadvantages of the individual studies, would in our opinion be the most rational approach when trying to answer this important clinical question. It is therefore reassuring that 3 studies, including 2 registry-based studies and 1 interview-based study, have now consistently found that use of nonaspirin NSAIDs seem not to be associated with an overall increased risk of ICH.\(^1\)\(^–\)\(^3\)\(^,\)\(^6\)

David Gaist, MD, PhD
Søren Bak, MD
Epidemiology
Institute of Public Health & Danish Twin Register
University of Southern Denmark
Department of Neurology
Odense University Hospital
Odense, Denmark


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Seppo Juvela

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