Editorial Commentary

Should Acetaminophen Be Added to the List of Anti-Inflammatory Agents That Are Associated With Cardiovascular Events?

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See related article, pp 1008–1014

Ever since the use of rofecoxib turned our attention toward the potential for adverse cardiovascular events associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), other NSAIDs and other anti-inflammatory agents have been scrutinized. More recently, attention has been turned toward acetaminophen. In 2006, Chan et al2 reported (from the Nurses Health Study) the association of acetaminophen with adverse cardiovascular events and found that although the use of NSAIDs or acetaminophen at high frequency or dose was associated with increased risk, moderate use did not confer a substantial risk. Chan et al2 also observed that cardiovascular event risk was greater in women than in men and in smokers compared with nonsmokers. Small studies also suggested small increases in blood pressure of a few mm Hg in acetaminophen users that at a population level could be important.2 The mechanism(s) for the increased cardiovascular risk has been linked to selective inhibition of cyclooxygenase, officially known as prostaglandin-endoperoxide synthase of which cyclooxygenase-2 is a subfamily. It was initially thought that acetaminophen had no effect on cyclooxygenase, but recent evidence suggests it may, particularly in higher doses. Although the exact mechanism(s) by which cyclooxygenase is inhibited in various circumstances is still subject to debate, it has been postulated that >2 cyclooxygenase variants exist.3 Cyclooxygenase-2 inhibitors have been found to increase the risk of atherothrombosis even with short-term use.4 A 2006 analysis of 138 randomized trials and almost 150 000 participants showed that selective cyclooxygenase-2 inhibitors are associated with a moderately increased risk of vascular events, mainly from a 2× increased risk of myocardial infarction, similar to high-dose regimens of some traditional NSAIDs.5 Limitations on the association of anti-inflammatory agents (although acetaminophen has been found not to have much anti-inflammatory activity) center around the lack of randomized controlled trials and the dependence on observational studies many of which are retrospective.6

In this issue, Fulton et al7 used the UK Clinical Practice Research Database (GPRD) to assess the association of acetaminophen with adverse cardiovascular events. The past decade has seen a surge in the use of computerized healthcare data for pharmacoepidemiologic study. Of all European databases, the GPRD has been one of the most widely used. This database belongs to the UK Department of Health and is maintained by the Office of National Statistics. Presently, ≈1500 general practitioners with a population coverage in excess of 3 million systematically provide their computerized medical data anonymously to Office of National Statistics. Validation studies of the GPRD have documented the recording of medical data into general practitioners’ computers to be near to complete. The GPRD collects truly population-based data, has a size that makes it possible to follow-up large cohorts of users of specific drugs, and includes both outpatient and inpatient clinical information.8 For this study, the data from the GPRD included all patients aged ≥65 years with a diagnosis of hypertension with at least 2 years of validated follow-up before 1996. The authors note that from age ≥65 years, patients in the United Kingdom do not pay prescription charges minimizing the risk of confounding by use of over-the-counter acetaminophen. After appropriate inclusion/exclusion criteria, the study population was 44 406 individuals. In their analysis, there was no evidence that acetaminophen was associated with myocardial infarction or stroke.

There are many limitations to their analysis. First, the authors make the assumption that because individuals aged ≥65 can get acetaminophen for free, they will be adequately represented in the analysis sample. However, because acetaminophen is inexpensive, many subjects might still buy it over-the-counter. Also, there is no assurance that because a prescription is filled that the drug is taken as prescribed, and many of the subjects were low-level users (defined as receiving a prescription in 25% or fewer of months during the 6.4-year mean follow-up). Of the 10 878 exposed, 276 (2.5%) were high users, 1250 (11.5%) were medium users, and 9352 (86.0%) were low users. Because other studies have suggested a dose-response effect, this could certainly limit the interpretation of no association. Interestingly, the authors report that event rates differed across exposure groups, and they were the highest in high-frequency users. Finally, the authors use propensity score matching to limit the potential for confounding. Large observational cohort studies are an important study design that is increasingly being used to estimate the effect of a pharmacological exposure in
a time-to-event analysis. Compared with randomized controlled trials, the gold-standard approach to the time-to-event studies, observational studies are prone to confounding. For the most part, increased chance of confounding in observation studies is caused by systematic differences in the distribution of baseline characteristics between treated and untreated subjects. Because of this fact, exposed study participants cannot be directly compared with the unexposed. Propensity score matching has become a popular statistical tool to make exposed and unexposed groups similar in baseline characteristics, minimize confounding, and estimate relationships with the outcome more accurately. Propensity score reflects the probability of receiving an exposure of interest based on a host of the baseline characteristics. Study participants matched on propensity are considered to be balanced in the distribution of the baseline characteristics and, thus, can be compared. Calculation of propensity becomes extremely important in a case when there are no data on the indications for the use of pharmacological agent, such as in this study of the association of acetaminophen use and cardiovascular outcomes.

Even with all advantages described above, propensity matching has limitations. Two important considerations in such an analysis are variable selection for propensity estimation models and propensity-matching diagnostics. The general guidance for the variables to be included into propensity score calculation is that researchers should be liberal in the covariate selection and include variables that are both associated and unassociated with the treatment. Some studies include >100 predictors to estimate the propensity score. Generally, the number of covariates included in propensity estimation is higher than the number of covariates adjusted for in a conventional analysis. The second concept of propensity-matching diagnostics reflects the fact that researchers want to know how well the exposed and unexposed groups were balanced after the matching is done. Usually, this is implemented by assessing the similarity of the covariate distribution between matched groups.

One of the strengths of the study by Fulton et al. is that they supplemented their main analyses with the acetaminophen use propensity estimation and conducted analyses on the matched subsample. The study group used the neighbor matching has a robust approach to the one-to-one matching. Fulton et al. have also attempted to provide both graphic and numeric diagnostics of the quality of the matching technique. The authors listed the following variables used in the calculation of the propensity score: age, sex, diabetes mellitus, statins, aspirin, and NSAID exposure without aspirin. Although there are no set rules for the variable selection for the matching, this article would benefit from a more detailed description of the conceptual framework that guided covariate selection. The list of these predictors seems to be less inclusive than those used in the main analyses. One would expect that UK Clinical Research Practice Datalink has a potentially wider covariate availability that may be useful in both matching and adjustment. For example, data on baseline blood lipids would be an appropriate included covariate. The fact that exposed and unexposed study participants were not matched on prevalent stroke and ischemic heart disease supports the notion that matching probably required the use of more covariates.

Despite the weaknesses of the study, this assessment of the lack of association of acetaminophen and cardiovascular outcomes should provide some comfort, until other studies support or refute the GRPD findings.

Disclosures

None.

References

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