Frequency of Analgesic Use and Risk of Hypertension Among Men

John P. Forman, MSc, MD; Eric B. Rimm, ScD; Gary C. Curhan, MD, ScD

Background: Nonnarcotic analgesics are the most commonly used drugs in the United States. To our knowledge, the association between the use of these analgesics, particularly acetaminophen, and the risk of hypertension among men has not been extensively studied.

Methods: The association between analgesic use and risk of incident hypertension was analyzed in a prospective cohort analysis of 16,031 male health professionals without a history of hypertension at baseline. Detailed information about the frequency of use of acetaminophen, nonsteroidal anti-inflammatory drugs, and aspirin was gathered at baseline and updated 2 years later. The relative risk of incident hypertension during 4 years of follow-up was analyzed using multivariable proportional hazards regression.

Results: We identified 1,968 incident cases of hypertension. After adjusting for multiple potential confounders, men who used acetaminophen 6 to 7 days per week compared with nonusers had a relative risk for incident hypertension of 1.34 (95% confidence interval, 1.00-1.79; \( P = .01 \) for trend). This same comparison resulted in relative risks of 1.38 (95% confidence interval, 1.09-1.75; \( P = .002 \) for trend) for nonsteroidal anti-inflammatory drugs and 1.26 (95% confidence interval, 1.14-1.40; \( P < .001 \) for trend) for aspirin. We observed similar results when the number of pills per week was analyzed rather than frequency of use in days per week.

Conclusions: The frequency of nonnarcotic analgesic use is independently associated with a moderate increase in the risk of incident hypertension. Given the widespread use of these medications and the high prevalence of hypertension, these results may have important public health implications.

Arch Intern Med. 2007;167:394-399
The 2000 biennial questionnaire queried participants about their use of acetaminophen, NSAIDs, and aspirin. These questions asked about usual frequency of use in days per week (0, 1, 2-3, 4-5, and 6-7) and number of pills consumed per week (0, 1-2, 3-5, 6-14, and ≥15). Information about past use was not gathered, and dose information was only asked for aspirin. Identical questions appeared on the 2002 biennial questionnaire, and exposure information was updated to reflect levels of analgesic use.

ASCERTAINMENT OF INCIDENT HYPERTENSION

Biennial mailed questionnaires ask participants to report whether a clinician made a new diagnosis of hypertension during the preceding 2 years. Self-reported hypertension was shown to be highly reliable in the Health Professionals Follow-up Study. Among a subset of men who reported hypertension, 100% had the diagnosis confirmed by medical record review. In addition, self-reported hypertension was highly predictive of subsequent cardiovascular events. A participant was considered to have prevalent hypertension and, thus, excluded if the participant reported this diagnosis on any questionnaire up to and including the 2000 questionnaire. Therefore, cases were individuals who first reported hypertension on subsequent questionnaires (2002 and 2004).

ASCERTAINMENT OF COVARIATES

Age, Body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters), smoking status, and physical activity were ascertained from the 2000 questionnaire and updated in 2002. Because dietary information from the food frequency questionnaire (including intakes of alcohol, folate, sodium, potassium, calcium, magnesium, and fiber) is available every 4 years (and not assessed in 2000), we imputed 1998 dietary information for 2000, and updated dietary data with the 2002 food frequency questionnaire. Information about these covariates has been validated compared with “gold standard” measures, with correlations ranging from 0.61 for potassium to 0.90 for alcohol. Family history of hypertension was available on the 1990 questionnaire. Participants reported their systolic and diastolic blood pressure (measured in millimeters of mercury) on the 2000 questionnaire. Participants reported their race on the 1986 questionnaire.

STATISTICAL ANALYSES

The frequency of use of a particular analgesic categorized in days per week (0, 1, 2-3, 4-5, and 6-7) was analyzed in the primary analyses, defining nonusers of that drug as the reference group. In secondary analyses, we examined number of pills consumed per week (0, 1-2, 3-5, 6-14, and ≥15), using 0 as the reference group. For each participant, person-months of follow-up were counted from the date of return of the first questionnaire to the mailing date of the last questionnaire, and allocated according to exposure status. Person-time was truncated when an event occurred. Participants were censored at the date of death or, if they did not return a subsequent questionnaire, at the date the subsequent questionnaire was mailed.

Age- and multivariable-adjusted relative risks (RRs) were calculated using Cox proportional hazards regression models. All RRs for acetaminophen, NSAIDs, and aspirin simultaneously controlled for use of the other analgesic types. Multivariable models were further adjusted for variables that have been proposed to be associated with hypertension (age [continuous], race [5 categories], BMI [continuous], physical activity [quintiles], smoking status [past, current, or never], family history of hypertension [yes or no], alcohol intake [6 categories], and intakes of folate, potassium, calcium, magnesium, and sodium [quintiles]). Secondary analyses excluding men who reported coronary heart disease at baseline were also performed. In additional analyses, we controlled for baseline systolic and diastolic blood pressure, and limited the analyses to the subset of men who reported having clinician examinations during the period of follow-up.

Because age and BMI are such powerful risk factors for hypertension, we investigated whether the association between analgesic use and hypertension varied according to age (<60, 60-70, and >70 years) or BMI (<25 or ≥25). Stratified multivariable analyses were performed, and appropriate interaction terms were generated to test whether interactions were statistically significant.

For all RRs, we calculated 95% confidence intervals (CIs). All P values are 2-tailed. Statistical tests were performed using SAS statistical software, version 9 (SAS Institute Inc, Cary, NC).

RESULTS

BASELINE CHARACTERISTICS

At baseline in 2000, the mean age of men in the analysis was 64.6 years (median, 63 years; interquartile range, 57-71 years) and the mean BMI was 24.8 (median, 25.1; interquartile range, 23.2-27.2). The baseline characteristics of these men, stratified by category of analgesic frequency, are shown in Table 1. A history of smoking was consistently more common with increasing analgesic intake; for other characteristics, the correspondence to analgesic use was not as consistent. For example, age, BMI, and folate intake were higher with increasing frequency of acetaminophen use, whereas level of physical activity was lower. In contrast, no variables seemed to consistently correspond to NSAID frequency; and with increasing aspirin frequency, physical activity level increased along with folate intake. Baseline blood pressure reporting did not seem to differ across medications.

FREQUENCY OF ANALGESIC USE

During 4 years and 52 673 person-years of follow-up, 1968 participants reported a new diagnosis of hypertension. We observed a significant independent association between frequency of analgesic use and risk of incident hypertension among all 3 analgesic classes (Table 2). Compared with nonusers, men who took acetaminophen 6 to 7 days per week had a multivariable RR for incident hypertension of 1.34. This same comparison yielded a RR of 1.38 for NSAIDs and a RR of 1.26 for aspirin.

Further adjustment for baseline systolic and diastolic blood pressure may be overcontrol, but we did so in secondary analyses. After adding baseline blood pressure to the multivariable models, the RR comparing men who used acetaminophen 6 to 7 days per week compared with nonusers was 1.31 (95% CI, 0.96-1.80; P=.05 for trend). The RR for NSAID use was 1.33 (95% CI, 1.02-1.74; P=.02 for trend), and the RR for aspirin use was 1.31 (95% CI, 1.17-1.47; P<.001 for trend). These estimates are not substantially different (<5% change) from models that did not include baseline blood pressure.
Because men who frequently use analgesics may visit their clinicians more often, thereby having a higher frequency of blood pressure measurements and correspondingly an increased chance of being diagnosed as having hypertension, we also examined only the subset of men who reported visiting their clinicians during follow-up (n=14,868). In this subset, the multivariable RR for 6 to 7 days per week of use compared with nonusers was 1.26 (95% CI, 0.94-1.70; P=.05 for trend) for acetaminophen, 1.35 (95% CI, 1.06-1.72; P=.008 for trend) for NSAIDs, and 1.23 (95% CI, 1.10-1.37; P<.001 for trend) for aspirin.

### Table 1. Characteristics of the Health Professionals Follow-up Study for Participants Without Baseline Hypertension in 2000*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acetaminophen Data</th>
<th>NSAID Data</th>
<th>Aspirin Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>14,036</td>
<td>12,580</td>
<td>8,598</td>
</tr>
<tr>
<td>Age, y</td>
<td>63 (57-71)</td>
<td>64 (57-72)</td>
<td>63 (56-71)</td>
</tr>
<tr>
<td>BMI, kg/m²†</td>
<td>25.1 (23.7-27.1)</td>
<td>25.1 (23.7-27.1)</td>
<td>25.1 (23.7-27.1)</td>
</tr>
<tr>
<td>Physical activity, METs/wk</td>
<td>27.5 (12.2-51.4)</td>
<td>26.3 (11.0-49.6)</td>
<td>26.2 (12.1-47.1)</td>
</tr>
<tr>
<td>Alcohol, g/d</td>
<td>6.4 (0.9-14.8)</td>
<td>5.8 (0.9-14.3)</td>
<td>5.5 (0.9-13.9)</td>
</tr>
<tr>
<td>Calcium, mg/d</td>
<td>900 (693-1224)</td>
<td>909 (695-1235)</td>
<td>889 (680-1212)</td>
</tr>
<tr>
<td>Magnesium, mg/d</td>
<td>391 (335-462)</td>
<td>392 (335-463)</td>
<td>385 (329-456)</td>
</tr>
<tr>
<td>Potassium, mg/d</td>
<td>3558 (3142-4022)</td>
<td>3566 (3142-4035)</td>
<td>3521 (3155-4028)</td>
</tr>
<tr>
<td>Folate, dfe/d</td>
<td>966 (542-1404)</td>
<td>977 (542-1408)</td>
<td>865 (519-1379)</td>
</tr>
<tr>
<td>Smoking status‡</td>
<td>Past</td>
<td>Past</td>
<td>Past</td>
</tr>
<tr>
<td>Past</td>
<td>39.2</td>
<td>39.0</td>
<td>38.1</td>
</tr>
<tr>
<td>Current</td>
<td>4.3</td>
<td>4.4</td>
<td>4.5</td>
</tr>
<tr>
<td>Family history of hypertension‡</td>
<td>31.6</td>
<td>31.6</td>
<td>31.1</td>
</tr>
</tbody>
</table>

Abbreviations: dfe, dietary folate equivalent; MET, metabolic equivalent task; NSAID, nonsteroidal anti-inflammatory drug.

*Data are given as median (interquartile range) unless otherwise indicated.
†Calculated as weight in kilograms divided by the square of height in meters.
‡Data are given as percentage of each group.

NUMBER OF ANALGESIC PILLS

We also examined the number of analgesic pills taken per week and the risk of incident hypertension; the results were similar to those when frequency of use was analyzed. For total number of analgesic pills, men who took 15 or more pills per week compared with men who took 0 had a multivariable RR of 1.48 (95% CI, 1.22-1.80; P<.001 for trend). Comparing men who took 15 or more pills per week of a particular analgesic with those who took 0, the multivariable RRs were 1.04 (95% CI, 0.61-1.76; P=.01 for trend) for acetaminophen, 1.33 (95%...
EFFECT MODIFICATION

The association between acetaminophen use and risk of incident hypertension was greater among men with a BMI of less than 25; among men with a BMI of 25 or more, the association was reduced and not significant (P = .01 for the interaction). In contrast, the association between NSAID frequency and risk of hypertension was greater among overweight and obese men, and diminished and not significant among men with a BMI of less than 25 (P = .01 for the interaction). No modification of the aspirin–hypertension association by BMI was observed (P = .94 for the interaction).

The association between NSAID or aspirin use and hypertension was not significantly modified by age (P = .16 for NSAIDs and P = .24 for aspirin for the interaction). The association between acetaminophen frequency and incident hypertension tended to be greater among men younger than 60 years compared with older men, but this was not statistically significant (P = .09 for the interaction).

Comments

Among 16,031 men not diagnosed as having hypertension, we observed that the frequency of acetaminophen, NSAID, and aspirin use was independently associated with the risk of incident hypertension.

The association between acetaminophen use and hypertension may be mediated through inhibition of vasodilatory prostaglandins, increases in cellular oxidative stress, and reduction of proper endothelial function. Acetaminophen produces its analgesic effect by inhibiting prostaglandin H2 synthase, the same enzyme that is the target of NSAIDs and aspirin. However, because acetaminophen blocks this enzyme at its peroxidase rather than cylooxygenase catalytic site, the tissue specificity differs from that of NSAIDs and aspirin. This explains why acetaminophen is an effective blocker of prostaglandin synthesis in endothelial cells and in the kidney, but is a less effective antiplatelet and anti-inflammatory agent. By producing its therapeutic action, acetaminophen free radicals are generated and are quenched by the consumption of glutathione. Endothelial prostaglandin inhibition and oxidative stress may lead to endothelial dysfunction, and acetaminophen might also inhibit nitric oxide formation through other mechanisms.

The associations between NSAIDs and aspirin and hypertension may also be due to inhibition of vasodilatory prostaglandins. In addition, NSAIDs lead to increased renal sodium and water reabsorption and may exert a deleterious effect on endothelial function by increasing endothelin-1 production.

Our findings of moderately increased risks are consistent with those of the Nurses’ Health Study; the multivariable RRs (95% CIs) comparing the highest with lowest frequency of use among the nurses were 1.20 (1.08–1.33) for acetaminophen, 1.35 (1.25–1.46) for NSAIDs, and 1.21
(1.13-1.30) for aspirin.21 The men in our study and the women in the Nurses’ Health Study24 are more similar in age (mean ages, 65 and 55 years) compared with the much younger Nurses’ Health Study II participants (mean age, 39 years).22 In the Nurses’ Health Study II, the association between frequency of acetaminophen (RR, 2.00; 95% CI, 1.52-2.62) and NSAID (RR, 1.86; 95% CI, 1.51-2.28) use and incident hypertension was considerably greater.22

Our findings are also consistent with the analysis of frequency of use in the Physicians’ Health Study.23 Although the investigators found a significant association only with frequency of acetaminophen intake, the highest intake category was 61 or more pills per year, which averages to approximately 1 to 2 pills per week.23 In the Physicians’ Health Study, men who estimated taking 61 or more NSAID pills per year compared with those who took 0 had a RR for hypertension of 1.01.23 In our study, the RR for men taking 1 to 2 NSAID pills per week compared with 0 was 0.99 (95% CI, 0.68-1.37), consistent with results from the Physicians’ Health Study. For aspirin, a similar argument can be made. The RR for 61 or more pills per year of aspirin was 1.08 in the Physicians’ Health Study and 1.11 (95% CI, 0.92-1.34) for 1 to 2 pills per week in our study.23

Other epidemiologic and small interventional studies have also examined the relation between analgesics and hypertension; most have focused on NSAIDs. Two community-based cross-sectional studies33,34 in elderly populations found significant associations between NSAID use (yes or no, rather than dose used) and hypertension, with odds ratios of 1.4 to 2.2, after adjusting for various potential confounders, such as age and BMI. A large case-control study35 of elderly Medicaid beneficiaries reported a 1.6-fold increased odds of filling an initial prescription for antihypertensive medication if an NSAID prescription was filled during the prior 60 days after controlling for age, sex, race, nursing home status, and health care use. Two meta-analyses36,37 of randomized trials reported that NSAIDs increased mean blood pressure. One found that, among 771 primarily white participants of various trials, NSAIDs increased mean blood pressure by 5 mm Hg overall (95% CI, 1.2-8.7 mm Hg).36 However, the effect was largely limited to those participants receiving therapy for existing hypertension (5.4–mm Hg increase; 95% CI, 1.2-9.6–mm Hg); among the studies of normotensive individuals, blood pressure increases with NSAIDs were small and not statistically significant. Furthermore, in the trials in which antihypertensive medicines were administered, NSAIDs antagonized the effect of these drugs.36 The second meta-analysis37 found a 3–mm Hg increase in mean blood pressure with NSAIDs that was also limited to participants with preexisting hypertension. In addition, only certain NSAIDs, such as indomethacin and naproxen, were associated with increased blood pressure, while others, such as ibuprofen and sulindac, were not.37 Taken together, these meta-analyses suggest that NSAIDs may antagonize the efficacy of antihypertensive medication.

Less information has been published concerning acetaminophen’s potential effect on blood pressure and risk of hypertension. A short-term randomized crossover study38 of 20 patients with treated hypertension reported that 1000 mg of acetaminophen given 4 times per day vs placebo for 4 weeks led to a statistically significant 4–mm Hg increase in systolic blood pressure. Aspirin has also received less attention. A prospective cohort study39 of 1040 women found a moderate but not statistically significant association between baseline aspirin use (determined by urinary salicylates) and incident hypertension during a 20-year period (odds ratio, 1.3; P=.11). In the 2 meta-analyses36,37 of NSAIDs previously mentioned, aspirin use was also examined; although slight increases in blood pressure were noted, the CIs were wide and not statistically significant.

We observed a stronger association between acetaminophen use and hypertension among leaner compared with heavier men; in contrast, the association between NSAIDs and hypertension was more pronounced in heavier compared with leaner men. The mechanisms that may underlie this finding are unclear. Higher BMI is associated with oxidative stress, endothelial dysfunction, and salt sensitivity.40-42 Thus, if the mechanisms through which BMI and analgesics are associated with hypertension overlap, then interactions between BMI and analgesics are likely to be complex. Although we did not find effect modification by age, the youngest person in our analysis was 55 years old. If, indeed, younger individuals are more susceptible to analgesics, as suggested by the results in younger women,22 then it is possible our age range was insufficiently broad to detect an interaction.

Our study has weaknesses and strengths that deserve mention. We did not directly examine participants during follow-up to confirm self-reported hypertension; however, all participants were health professionals, and hypertension reporting has previously been shown to be reliable.23 Also, it was possible that men taking analgesics were more likely to visit their clinicians and, thus, more likely to be diagnosed as having hypertension. Nevertheless, most men in this study (92.7%) reported at least 1 clinician visit during follow-up, and after limiting our analysis to this subset, the results were similar. Random misclassification of analgesic use may have occurred because of variable analgesic use in time and, hence, imprecise categorization, but such misclassification in this prospective study would have, if anything, led to an underestimation of the true association. Residual confounding is always a potential concern in observational studies, but we used reliable information on many known hypertension risk factors to carefully adjust our multivariate models; furthermore, we are unaware of common medical conditions that are simultaneously indications for analgesic use and independently associated with hypertension.

These data add further support to the hypothesis that nonnarcotic analgesics independently elevate the risk of hypertension. Given their common consumption and the high prevalence of hypertension, our results may have substantial public health implications, and suggest that these agents be used with greater caution. The contribution of nonnarcotic analgesics to the hypertension disease burden merits further study.

Accepted for Publication: November 10, 2006. Correspondence: John P. Forman, MSc, MD, Channing
Laboratory, 181 Longwood Ave, Third Floor, Boston, MA 02115 (jiforman@partners.org).

Author Contributions: Dr Forman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.


Financial Disclosure: None reported.

Funding/Support: This study was supported by scientist development grant 0535401 from the American Heart Association and by grants HL 35464 and CA 550750 from the National Institutes of Health.

Role of the Sponsor: The funding bodies had no role in data extraction and analyses, in the writing of the manuscript, or in the decision to submit the manuscript for publication.

REFERENCES