Use of Acetaminophen and Nonsteroidal Anti-inflammatory Drugs

A Prospective Study and the Risk of Symptomatic Diverticular Disease in Men

Walid H. Aldoori, MD; Edward L. Giovannucci, MD; Eric B. Rimm, ScD; Alvin L. Wing, MBA; Walter C. Willett, MD

Objective: To examine prospectively the relationship between self-reported regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen and the risk of symptomatic diverticular disease.

Design: Prospective cohort study using a mailed baseline questionnaire in 1986, and follow-up every 2 years through 1992.

Setting: Male health professionals residing in 50 US states.

Patients: A total of 35,615 male health professionals (dentists, optometrists, veterinarians, physicians, pharmacists, osteopathic physicians, podiatrists) 40 to 75 years of age at baseline and free of diagnosed diverticular disease, colon or rectal polyp, ulcerative colitis, and cancer prior to 1988.

Main Outcome Measures: Follow-up questionnaires in 1988, 1990, and 1992 about use of NSAIDs, acetaminophen, and other variables including the diagnosis of symptomatic diverticular disease.

Results: During 4 years of follow-up, we documented 310 newly diagnosed cases of symptomatic diverticular disease. After adjustment for age, physical activity, and energy-adjusted dietary fiber and total fat intake, regular and consistent use of NSAIDs and acetaminophen was positively associated with the overall risk of symptomatic diverticular disease (for users vs nonusers, relative risk [RR] for NSAIDs = 2.24, 95% confidence interval [CI], 1.28-3.91; RR for acetaminophen = 1.81, 95% CI, 0.79-4.11). Most of this positive association was attributable to cases associated with bleeding, particularly for acetaminophen (for users vs nonusers, RR for NSAIDs = 4.64, 95% CI, 0.99-21.74; RR for acetaminophen = 13.63, 95% CI, 3.53-52.60).

Conclusions: These results suggest that regular and consistent use of NSAIDs in general and acetaminophen is associated with symptoms of severe diverticular disease, particularly bleeding. Further research is needed to investigate the potentially deleterious effect of NSAIDs and other medications on the lower gastrointestinal tract.

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DIVERTICULAR DISEASE is one of the most common disorders of the colon among the elderly in western societies and it is estimated to occur in one third of all persons older than 45 years and in two thirds of all persons older than 85 years. In most cases the condition is asymptomatic, and only between 10% and 25% of affected individuals develop symptoms. The predominant symptoms are abdominal pain, change in bowel habits, bleeding, and perforation. Symptomatic diverticular disease results in 200,000 hospitalizations in the United States annually.

Earlier this century diverticular disease was widely believed to be rare and was regarded as a pathological curiosity. This prompted Burkitt and Painter to call it “a 20th century problem” or “a disease of Western civilization” in contrast to its rarity in many developing countries. This sharp contrast was largely attributed to dietary differences, mainly in the decline in the intake of dietary fiber from cereal grains. The dietary fiber hypothesis is supported by human and animal studies. Previous case-control studies have found that patients consumed less fiber than noncases, and similar findings as well as a beneficial effect of physical activity were observed in the prospective Health Professionals Follow-up Study.

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Considering that most cases of diverticular disease are asymptomatic, it is important to study the possible factors that might determine the development
PARTICIPANTS AND METHODS

STUDY POPULATION

The Health Professionals Follow-up Study is a prospective study of heart disease and cancer among 51,529 US male health professionals who reside in 50 states in the United States and were 40 to 75 years old in 1986. The study population consists of 29,683 dentists, 3745 optometrists, 2218 osteopathic physicians, 4185 pharmacists, 1600 podiatrists, and 10,098 veterinarians. The study began in 1986 when cohort members completed a detailed food-frequency questionnaire that was validated in this cohort. It also provided information about medical history, age, weight, height, smoking, alcohol consumption, physical activity, use of acetaminophen, nonaspirin NSAIDs, and other medications, and a history of professionally diagnosed medical conditions. Every 2 years (1988, 1990, and 1992) follow-up questionnaires were sent to update information on potential risk factors and to identify newly diagnosed cases of various diseases. The 1990 and 1992 follow-up questionnaires contained specific questions regarding diverticular disease.

Current use of acetaminophen, NSAIDs, and other relevant medications was assessed at baseline in 1986 and from responses on 1988 and 1990 follow-up questionnaires using a list that included the following categories: (1) acetaminophen, more than 2 times per week (eg, Tylenol); (2) aspirin, more than 2 times per week (eg, Anacin, Bufferin, Alka-Seltzer); (3) other anti-inflammatory medications (eg, Motrin, Indocin, Naprosyn, Dalboid); and (4) steroids taken orally (eg, Prednisone, Decadron, Medrol). Reasons for use, dosage, duration, and whether these medications were prescribed or obtained over the counter were not assessed at baseline.

IDENTIFICATION OF DIVERTICULAR DISEASE CASES

Follow-up questionnaires were sent in 1988, 1990, and 1992 to all study participants. On the 1990 and 1992 questionnaires, we asked whether diverticular disease had been diagnosed during the previous 2 years (diverticular disease was not a specified end point in the 1988 follow-up questionnaire). After up to 6 mailings for each follow-up period, the average response rate has been 94.1%. When diverticular disease was reported on the follow-up questionnaire, we mailed the cohort member a supplementary questionnaire to confirm the reporting and to ascertain the date of diagnosis, the presence and nature of any symptoms, the procedure performed to confirm the diagnosis (eg, barium study or endoscopy), treatment prescribed, and whether there were any dietary changes induced by symptoms that occurred prior to the diagnosis. We obtained 182 medical records from a sample of participants reporting diverticular disease to assess the validity of self-reporting and to ascertain the site of the diverticula. The records confirmed the self-reporting in 93% of the cases. We therefore accepted the other self-reports of diverticular disease as valid. Also, 96% of the cases were located in the descending colon (sigmoid, descending, or midtransverse), as expected in a predominantly white population. In the population eligible for analysis, we identified 310 newly diagnosed cases of symptomatic diverticular disease. Of these, 230 had abdominal pain or change in bowel habits as the major presenting symptoms and 80 had bleeding or fecal occult blood as their major presenting symptoms.

STATISTICAL ANALYSIS

A priori we excluded from this analysis men whose average daily energy intake, calculated from the food-frequency questionnaire, was outside the range of 3347 to 17,572 kJ (7960 to 4000 kcal) and those who left blank 70 or more food items on the dietary questionnaire. We also excluded men who reported previous cancer (other than nonmelanoma skin cancer), colon or rectal polyp, ulcerative colitis, and diverticular disease prior to 1988. After exclusions, the baseline population with complete information on the use of medications consisted of 35,615 men eligible for this analysis.

For each participant, follow-up time was calculated as the period beginning at the month of return of the 1988 questionnaire, and ending at the date of diagnosing diverticular disease, death, or to January 31, 1992, whichever came first. The relative risk (RR)—the incidence among the men in the exposure category (eg, regular use of acetaminophen or NSAIDs) divided by the corresponding rate in the reference category (nonusers)—was used as the measure of association. We used the Mantel-Haenszel summary estimator and proportional hazards modeling to adjust for age with the use of 5-year categories and for potentially confounding variables. These variables included physical activity and energy-adjusted dietary fiber and total fat intake. The P values are all 2 tailed, and for all RRs, we calculated 95% confidence intervals (CIs).

and severity of the symptomatic presentation of this disease, which are not well understood. Several reports have suggested an association between consumption of steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and the complications of diverticular disease. The NSAIDs are among the most widely used medications in the world. Because their use is particularly frequent among the elderly, and diverticular disease is common in this age group, even modest changes in the risk of side effects may have important public health implications. It is generally accepted that aspirin and NSAIDs have a deleterious effect on the upper gastrointestinal tract, where their use predisposes to the complications of peptic ulceration such as hemorrhage and perforation. Only recently, however, have NSAIDs been suggested to be harmful to the lower gastrointestinal tract. Little information exists about the adverse effects, if any, on the lower gastrointestinal tract with the regular use of either aspirin or acetaminophen. Also, most studies of medication use in relation to diverticular disease have been limited by the number of subjects, failure to adjust for potential risk factors such as dietary fiber, other dietary and nondietary factors such as physical activity, and the possibility of recall and selection bias in case-control studies. We report herein the results from a prospective study addressing the association between self-reported regular use of NSAIDs, acetaminophen, oral steroids, and as-
pirin and the diagnosis of symptomatic diverticular disease among men in the United States.

RESULTS

During 135,931 person-years of follow-up during a 4-year period between 1988 and 1992, 310 cases of symptomatic diverticular disease with complete information on the use of medications were documented in this cohort. Abdominal pain, change in bowel habits, bleeding, and fecal occult blood were the predominant self-reported symptoms for the disease.

Table 1 presents selected characteristics of the participants according to use of nonaspirin NSAIDs and acetaminophen in 1988. Men who reported regular use of NSAIDs were slightly heavier, more physically active, likely to smoke slightly more, more likely to have an endoscopic procedure, and more likely to use multivitamin tablets compared with nonusers. Similar patterns were observed among regular acetaminophen users; however, regular acetaminophen users were less physically active than nonusers. Dietary patterns were similar, but consumption of alcoholic beverages was slightly higher among NSAID users and slightly lower among acetaminophen users. The self-reported rates of use did not differ substantially during the 1988 and 1990 follow-up period for both acetaminophen and NSAIDs.

We observed an overall increased risk for symptomatic diverticular disease among regular NSAID and acetaminophen users compared with nonusers (RR for NSAID users = 2.27, 95% CI, 1.24-4.17) and acetaminophen users = 1.40, 95% CI, 0.93-2.13). As shown in Table 2, the positive association between NSAID and acetaminophen use and the risk of symptomatic diverticular disease became stronger with evidence of more consistent use of both medications, ie, regular use of both medications reported on both the 1988 and 1990 questionnaires. The RR did not change appreciably when we controlled for risk factors, physical activity, and energy-adjusted dietary fiber and total fat intake (all in quintiles) (Table 2).

We further explored the association between the use of NSAIDs and acetaminophen and the risk of symptomatic diverticular disease by specific presenting symptoms. We observed an increased risk of symptomatic diverticular disease among cases in which the participants’ symptoms were mainly abdominal pain and change in bowel habits, particularly with evidence of more consistent use of NSAIDs (RR = 2.27, 95% CI, 1.24-4.17) (Table 3). Such a positive association was not observed among regular acetaminophen users (RR = 1.17, 95% CI, 0.37-3.69) (Table 3). We also observed an increased risk of symptomatic diverticular disease with regular and consistent use of NSAIDs and acetaminophen among the patients whose presenting symptoms were

<table>
<thead>
<tr>
<th>Table 1. Selected Characteristics of Study Participants by Reported NSAID and Acetaminophen Use in 1988*</th>
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<tbody>
<tr>
<td>Characteristics</td>
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<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>No. of participants</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Body mass index, kg/m²</td>
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<tr>
<td>Current smokers, %</td>
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<td>Endoscopy during study, %</td>
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<td>Multivitamin users, %</td>
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<td>Leisure time physical activity, metabolic equivalents/wk</td>
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<tr>
<td>Mean daily intake†</td>
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<td>Total fat, g</td>
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<td>Total energy intake, kJ/d</td>
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<td>Alcohol, g</td>
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<td>Dietary fiber, g</td>
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*Characteristics were age standardized to the age distribution of the entire cohort. NSAID indicates nonsteroidal anti-inflammatory drug.
†Dietary variables were computed using the food-frequency questionnaire completed by participants at baseline in 1986.

<table>
<thead>
<tr>
<th>Table 2. Relative Risk for Symptomatic Diverticular Disease by Use of NSAIDs and Acetaminophen in the Health Professionals Follow-up Study</th>
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<tbody>
<tr>
<td>Variable</td>
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<tr>
<td>NSAID*</td>
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<td>Users, cases/person-years</td>
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<tr>
<td>Age-adjusted RR (95% CI)‡</td>
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<td>Multivariate RR (95% CI)§§</td>
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<td>Acetaminophen</td>
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<td>Users, cases/person-years</td>
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<tr>
<td>Age-adjusted RR (95% CI)‡</td>
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<tr>
<td>Multivariate RR (95% CI)§§</td>
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*Does not include aspirin. NSAID indicates nonsteroidal anti-inflammatory drug.
†Participants who reported the use of NSAIDs and acetaminophen (the follow-up period for 1988 was 1988-1992; for 1988 and 1990, 1990-1992); nonusers reported no use of NSAIDs or acetaminophen during the specified time periods.
‡Age-adjusted relative risk (RR) and 95% confidence interval (CI) for users compared with nonusers of NSAIDs or acetaminophen for each of the specified time periods.
§Relative risk adjusted for age, physical activity, and energy-adjusted dietary fiber and total fat.

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mainly bleeding. This positive association was substantially, particularly among regular and consistent acetaminophen users (RR = 13.63, 95% CI, 3.53-52.60) (Table 4). The positive association of acetaminophen was further strengthened when we excluded from our analysis participants with known upper gastrointestinal tract conditions associated with bleeding (such as gastric or duodenal ulcers), or with a history of liver diseases (RR for acetaminophen users = 18.65, 95% CI, 4.63-75.10). Moreover, when we considered the cases diagnosed in the last 2 years of our follow-up in which the participants reported regular acetaminophen use on the 1986 baseline questionnaire and also on the consecutive follow-up questionnaires in 1988 and 1990, the positive association of acetaminophen use with the risk of bleeding diverticula was further increased (RR = 27.30, 95% CI, 11.42-65.24). However, the risk of symptomatic presentation of diverticula in general, and of bleeding in particular, was not as substantially elevated for NSAID users who reported regular intake on only one of the follow-up questionnaires, and who were diagnosed within the corresponding 2-year follow-up period (RR of bleeding for self-reported NSAIDs users on the 1988 and 1990 questionnaires = 1.48, 95% CI, 0.44-4.99 and RR = 2.81, 95% CI, 0.83-9.48, respectively; RR of bleeding for acetaminophen users = 1.73, 95% CI, 0.42-7.18 and RR = 8.48, 95% CI, 3.21-22.43, respectively). The association between the use of NSAIDs and acetaminophen and the risk of bleeding was higher among regular and consistent users who were younger than 65 years than it was for those who were older than 65 years (for users younger than 65 years, RR for NSAID users = 6.00, 95% CI, 1.22-29.46; RR for acetaminophen users = 9.90, 95% CI, 1.98-49.37). The use of NSAIDs and acetaminophen was not associated with an elevated risk of fecal occult blood. We did not observe any increase in the risk of symptomatic diverticular disease among regular and consistent aspirin users (RR for overall symptoms = 0.80, 95% CI, 0.55-1.18; RR for abdominal pain and change in bowel habits = 0.78, 95% CI, 0.50-1.21; RR for fecal occult blood = 1.29, 95% CI, 0.47-3.48; RR for bleeding = 0.60, 95% CI, 0.12-2.93). This association was generally similar between men younger than or older than 65 years. We observed an elevated risk of symptomatic diverticular disease among patients who reported regular and consistent use of oral steroids, particularly among the cases in which participants presented with abdominal pain and change in bowel habits. However, too few men among this cohort were taking oral steroids consistently to provide stable estimates (RR for abdominal pain and change in bowel habits = 2.16, 95% CI, 0.29-11.53).

When we included the use of NSAIDs and acetaminophen simultaneously in a multivariate model with age, physical activity, and energy-adjusted dietary fiber and total fat intake, our findings for participants who had bleeding were attenuated for NSAID and acetaminophen use, although this remained statistically significant for acetaminophen (RR for bleeding among NSAID users = 2.79, 95% CI, 0.56-13.83; RR among acetaminophen users = 10.74, 95% CI, 2.63-43.93). When we further included aspirin and oral steroids to the previous model, our findings for participants who had bleeding were attenuated for NSAID and acetaminophen use, but were not as substantial as estimated.
Lytic action on the gut mucosa, as in the case with fen-
fect of NSAIDs could be unrelated to their influence on
particularly with alcohol intake, have been reported,47,48
plications23,40 so that bleeding might occur in the presence
diverticula. Also, NSAIDs might inhibit platelet aggre-
glandin effects by NSAIDs might impair the ability of
the colon to limit inflammatory processes occurring within
d diverticular disease is predominantly right sided.54-56
mental use of NSAIDs and acetaminophen is associated with
symptoms of complicated diverticular disease, such as bleed-
Our study differed from previous reports by the avail-
ability of information about potentially confounding fac-
tors, such as dietary factors, alcohol intake, body mass
index, and physical activity, that were assessed and up-
dated at different follow-up periods and controlled for.
Also, use of NSAIDs, acetaminophen, and other related
medications that might cause similar adverse effects (such
as steroids) was assessed at several times throughout the
study; furthermore, 2 separate assessments of the use of
NSAIDs and acetaminophen allowed comparisons be-
tween long-term consistent users and nonusers. Fi-
nally, the relatively homogeneous background of par-
ticipants in the Health Professionals Follow-up Study
increases the likelihood of accurate exposure and out-
come reporting and decreases the likelihood of residual
confounding.17,19,30,31

Because we relied mainly on self-report of diverticu-
lar disease rather than complete medical records for all the
positive respondents, we could not exclude right-sided di-
verticulosis from our cases. However, among the 108 par-
ticipants for whom we obtained medical records that speci-
fied the diverticular site, exclusive right-sided diverticulosis
was present in less than 4%, which is what is expected in
a western population.32 This is in contrast to Asia where
diverticular disease is predominantly right sided.54,56

Biased recall of the use of medications was unlikely
because the data on reporting the use of medications
were collected before the diagnosis of symptomatic
diverticular disease. This study is limited by absence of
data on duration and dosage of NSAIDs and acetami-
phen. Because we assessed NSAIDs as a class and not as
individual agents, the risk presented in this study
should be considered as an overall risk. Although
adverse effects have been reported with the use of most
NSAIDs, there appear to be differences in risk among
different agents, with risks being particularly associated
with mefenamic acid, indomethacin, and diclofenac.49
Risk in our study might be underestimated since the
assumption of continuous use will not be perfectly true.
However, the prospective design of this study means
that any misclassification would be random with regard
to case status, and hence would tend to attenuate any
association. Our findings are most directly generalizable
to US men aged 40 years and older. Apart from reports
of higher preponderance of diverticular disease in wom-
en,2 we have no reason to believe that the relations we
observed in men would be different. In almost all the
studies that investigated NSAIDs and gastrointestinal
outcomes in general, there were no differences in the
risk by gender.27

Our findings suggest that regular and consistent use
of NSAIDs and acetaminophen is associated with symp-
toms of complicated diverticular disease, such as bleed-
ing, particularly with the use of acetaminophen. Fur-

These prospective data suggest that regular and consist-
ent use of NSAIDs and acetaminophen is associated with
an elevated risk of symptomatic diverticular disease, par-
ticularly for the patients who present with bleeding.

The findings for NSAID use and the risk of bleed-
ing of diverticula in this study concur with the findings
of other reports.20-24 Our findings could have arisen if the
symptoms (such as bleeding) were related to an under-
lying condition for which NSAIDs were used. This pos-
sibility is unlikely because we have eliminated many con-
ditions that might be associated with abdominal symptoms
(such as pain or bleeding), and, in view of their known
effects on the stomach and duodenum, it is unlikely that
NSAIDs would be used for abdominal symptoms. Rather
they are the most widely used agents to treat musculo-
skeletal and arthritic conditions,35 which are not gener-
ally known to be associated with such symptoms. Most
NSAIDs inhibit the action of prostaglandin synthet-
ase,36 which is believed to be responsible for some of these
complications, since prostaglandin may exert a gastro-
intestinal cytoprotective effect that is abolished with the
use of these medications.20,22,37-39 This inhibition of pro-
taglandin effects by NSAIDs might impair the ability of
the colon to limit inflammatory processes occurring within
diverticula. Also, NSAIDs might inhibit platelet aggre-
gation33,30 so that bleeding might occur in the presence
of a bowel lesion (such as a diverticulum). Alternatively,
or in addition, they may mask symptoms so that patients
present with more advanced disease.22,23 However, the
effect of NSAIDs could be unrelated to their influence on
prostaglandin synthetase and could exert a direct cyto-
lytic action on the gut mucosa, as in the case with fen-
mates that are associated with mild colitis,41,42 and other
NSAIDs that can occasionally cause ulcerative proctitis or
colitis.43 Furthermore, animal studies indicate that NSAID-
induced intestinal lesions could be influenced by intesti-
nal flora,44 food,45 and the enterohepatic circulation.46

In our study, the regular and consistent use of acet-
aminophen was associated with an elevated risk of di-
verticular bleeding, and this risk remained elevated even
when we adjusted for the use of other medications. This
finding was unexpected since acetaminophen is often con-
sidered as an attractive alternative analgesic to many in-
flammation medicines. As steroids) was assessed at several times throughout the
study; furthermore, 2 separate assessments of the use of
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