A BRIEF ORIGINAL CONTRIBUTION

No Association between Calcium Channel Blocker Use and Confirmed Bleeding Peptic Ulcer Disease

Walter E. Smalley, Wayne A. Ray, James R. Daugherty, and Marie R. Griffin

Calcium channel antagonists are commonly used drugs that have recently been reported to be associated with an increased incidence of gastrointestinal hemorrhage. We performed a retrospective cohort study among 105,824 enrollees of the Tennessee Medicaid program 65 years of age or older between 1984 and 1986. Exposure to calcium channel blockers and other medications was determined from pharmacy files. Hospitalization for bleeding peptic ulcers was identified by hospital claims and verified by a review of the medical record. Univariate estimates of relative risk for current users of calcium channel blockers and beta-blocker users were 1.8 (95% confidence interval (CI) 1.2-2.7) and 1.1 (95% CI 0.7-1.6) (reference group was nonuse of either). After adjustment for potential confounders, the relative risks for bleeding peptic ulcer among current users of calcium channel blockers and beta blockers were 1.1 (95% CI 0.7-1.7) and 1.0 (95% CI 0.7-1.6), respectively, when compared with those who used neither drug. In this population, after controlling for important confounders, there was no increased risk for hospitalization with bleeding peptic ulcer among users of calcium channel blockers. Am J Epidemiol 1998;148:350-4.

The calcium channel antagonists are frequently used in the management of hypertension and angina and accounted for over 41 million prescriptions dispensed in the United States during 1989 (1). A recent study reported a relative risk of 1.86 (95 percent confidence interval (CI) 1.22–2.82) for gastrointestinal bleeding among patients using calcium channel blockers compared with users of beta blockers (2). Similar results were reported in a smaller case-control study (3). Given the wide utilization of these drugs, even a small increase in risk would have important public health implications. To evaluate this further, we performed a retrospective cohort study of the relation between calcium channel blocker use and hospitalization for bleeding peptic ulcer disease among 105,824 persons aged 65 years or older who were Tennessee Medicaid enrollees between 1984 and 1986.

MATERIALS AND METHODS

Sources of data

The study population was drawn from the Tennessee Medicaid program, which, at the time of the study, had an annual enrollment of approximately 85,000 persons 65 years of age or older, accounting for 15 percent of the state’s elderly population. Administrative (claims) files of the Tennessee Medicaid program were the primary sources of data (4). The Medicaid enrollment file identifies persons who are eligible to receive Medicaid benefits; the specific dates of Medicaid coverage; and the sex, race, date of birth, and the county of residence of the enrollees. Linked Medicare-Medicaid hospital files include admission and discharge dates for hospitalizations and are coded by diagnosis according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (5) (up to six diagnoses in Medicare). The pharmacy file contains reimbursed prescriptions for outpatients and nursing home residents. During the study, most prescription drugs were included on the Medicaid formulary. This file identifies when the pre-

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scription was filled, which drug was dispensed, how much of the drug was dispensed, and the number of days the drug supply should last. The nursing home file includes the beginning and ending date of each nursing home stay that was reimbursed by Medicaid. Tennessee state death certificate files, which include the ICD-9-CM-coded underlying cause of death, have been linked with the Medicaid enrollment file.

Cohort
We studied a cohort of Tennessee Medicaid enrollees defined for previously reported studies of peptic ulcer disease (4, 6–10). Cohort members were Medicaid enrollees aged 65 years or older during the study period with at least 1 year of enrollment between January 1, 1984, and December 31, 1986.

Prescription drug exposure
Exposure to study drugs was determined from the Medicaid pharmacy file. Study calcium channel blockers were nifedipine, verapamil, and diltiazem. Current use of calcium channel blockers extended from the day the prescription was filled through the end of the days’ supply of drug as recorded by the pharmacist (usually 30 days). Nonuse of calcium channel blockers included person-time at least 365 days after the last period of current use. Use of beta blockers (propranolol, labetalol, nadolol, atenolol, metoprolol, acebutolol, and pindolol) and other prescription medications was similarly defined.

To examine the effect of calcium channel blockers by dose, we first calculated a “daily dose” by dividing the dose prescribed by the number of days’ supply of drug as recorded by the pharmacist (usually 30 days). Nonuse of calcium channel blockers included person-time at least 365 days after the last period of current use. Use of beta blockers (propranolol, labetalol, nadolol, atenolol, metoprolol, acebutolol, and pindolol) and other prescription medications was similarly defined.

Study events
The outcome of interest was hospitalization for bleeding peptic ulcer disease that included gastric or duodenal ulcer associated with hematemesis or melena as well as hospitalization for hematemesis in which the cause was undetermined.

The first qualifying hospitalization in the study period was identified by either a Medicaid hospital claim or death certificate indicating a diagnosis of peptic ulcer (ICD-9-CM codes 531–534), other disorders of the stomach and duodenum (codes 536 and 537), or gastrointestinal hemorrhage (code 578). A trained nurse reviewed the medical record of each hospitalization and recorded the relevant diagnostic information as well as information regarding the patient’s past ulcer history, ethanol use, and tobacco use. Of the 4,195 cohort members initially screened, 1,369 patients were confirmed to have peptic ulcer disease on the basis of medical record review (9, 10). Of these, 661 patients who presented with melena or hematemesis were considered to have bleeding peptic ulcer disease and are the focus of this study.

Analysis
Univariate rates of bleeding peptic ulcer disease were calculated by dividing the number of events by person-time. Adjusted relative risks were estimated by Poisson regression models using SAS PROC GENMOD (11). In this analysis, the primary comparison was between current calcium channel blocker use or current beta-blocker use and person-time with no current or recent use of either drug. To control for potential confounding, we evaluated regression models that included terms for demographic characteristics (age, sex, race, nursing home residence), current use of other drugs associated with upper gastrointestinal bleeding (nonsteroidal antiinflammatory agents, oral corticosteroids, oral anticoagulants, antineoplastic drugs), and comorbidity indicated by recent use of medical care (prior cardiac and noncardiac hospitalizations and oral nitrate use). Inclusion of terms for county size, thiazide use, other antihypertensive use, and prior use of diabetic agents, psychotropics, bronchodilators, antibiotics, other cardiovascular drugs, and “all other drugs” did not materially affect the relative risk estimates.

Differences in characteristics among the exposure groups were evaluated by chi-square analysis. All $p$ values were two sided.

RESULTS
The cohort included 105,824 individuals with 215,364 person-years of follow-up. There were 4,667 person-years of current calcium channel blocker use, 7,602 person-years of current beta-blocker use, and 183,927 person-years when neither drug was used (table 1). The remaining 19,168 person-years that included person-time with current use of both drugs together or recent use of either drug were excluded from the primary analysis.

The study population (table 1) included a high proportion of females (74 percent), blacks (25 percent),
TABLE 1. Characteristics of Tennessee Medicaid recipients, aged 65 years or older, 1984–1986

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Nonsteroidal antiinflammatory drug use (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of person-years</td>
<td>(Female; &gt;85 years; Black; Nursing home resident)</td>
</tr>
<tr>
<td>Current use of calcium channel blockers</td>
<td>Current use of beta blockers</td>
</tr>
<tr>
<td>4,667</td>
<td>74†</td>
</tr>
<tr>
<td>7,602</td>
<td>81‡</td>
</tr>
<tr>
<td>183,927</td>
<td>74</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Annual prevalence (%)</th>
<th>Bleeding ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use other drugs associated with gastroduodenal bleeding*</td>
<td>Use oral nitrates</td>
</tr>
<tr>
<td>Any noncardiovascular hospitalization</td>
<td>Any cardiovascular hospitalization</td>
</tr>
<tr>
<td>No. of persons</td>
<td>% with transfusion</td>
</tr>
<tr>
<td>Rate of hospitalization per 1,000 person-years</td>
<td></td>
</tr>
</tbody>
</table>

| Current use of calcium channel blockers | Current use of beta blockers | No use of either drug |
| 41‡ | 19‡ | 31‡ | 37‡ | 25 | 88 | 5.36 |
| 2‡ | 10‡ | 24 | 12‡ | 24 | 100 | 3.16 |
| 1.6 | 3 | 23 | 8 | 540 | 80 | 2.94 |

* Corticosteroids, coumadin, antineoplastic agents.
† Different from current beta-blocker users, p < 0.001.
‡ Different from nonusers, p < 0.001.

and those older than 85 years (18 percent). Current calcium channel blocker users were more likely than were current beta-blocker users to be male, to be 85 years of age or older, to be using nonsteroidal antiinflammatory drugs or other drugs that cause upper gastrointestinal bleeding, and, as indicated by recent use of medical care, to have higher levels of comorbidity (table 1).

The rates of hospitalization for bleeding peptic ulcer among users of calcium channel blockers and of beta blockers were 5.4 and 3.2 per 1,000 person-years, respectively (table 1). When compared with nonusers of either drug, the respective univariate relative risks among current calcium channel blocker users and beta-blocker users were 1.8 (95 percent CI 1.2–2.7) and 1.1 (95 percent CI 0.7–1.6) (table 2). For current calcium channel blocker users, the relative risk decreased as models that adjusted for more patient characteristics were used (table 2): 1.8 (95 percent CI 1.2–2.7) for demographic characteristics, 1.5 (95 percent CI 1.0–2.2) for other drugs that cause upper gastrointestinal bleeding, and 1.1 (95 percent CI 0.7–1.7) for comorbidity indicators. The relative risk estimates for current beta-blocker users were minimally

TABLE 2. Use of calcium channel blockers and beta blockers and risk of upper gastrointestinal hemorrhage, Tennessee Medicaid recipients, aged 65 years or older, 1984–1986

<table>
<thead>
<tr>
<th>Terms in Poisson regression model</th>
<th>Current calcium channel blocker use</th>
<th>Current beta-blocker use</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR*</td>
<td>95% CI*</td>
<td>RR</td>
</tr>
<tr>
<td>Univariate</td>
<td>1.8</td>
<td>1.2–2.7</td>
</tr>
<tr>
<td>Demographic characteristics only†</td>
<td>1.8</td>
<td>1.2–2.7</td>
</tr>
<tr>
<td>Above plus drugs associated with gastroduodenal bleeding‡</td>
<td>1.5</td>
<td>1.0–2.2</td>
</tr>
<tr>
<td>Above plus comorbidity indicators§</td>
<td>1.1</td>
<td>0.7–1.7</td>
</tr>
</tbody>
</table>

* RR, relative risk; CI, confidence interval.
† Demographic characteristics tested included age, race, sex, and residence at home or in nursing home.
‡ Ulcer-causing drugs included nonsteroidal antiinflammatory agents, oral corticosteroids, oral anticoagulants, antineoplastic drugs.
§ Comorbidity as indicated by recent use of medical care (prior cardiac and noncardiac hospitalizations and oral nitrate use).
affected by this process, decreasing to 1.0 (95 percent CI 0.7–1.6) for the final model. In the subgroup with no history of cardiovascular hospitalizations in the previous year, the adjusted relative risk among current calcium channel blocker users and beta-blocker users was 1.3 (95 percent CI 0.7–2.2) and 1.2 (95 percent CI 0.8–1.9), respectively.

There was no statistically significant increase of upper gastrointestinal bleeding among current users of any of the three specific calcium channel blockers nor did risk increase with dose. The estimates of risk among those on diltiazem, verapamil, and nifedipine were 0.7 (95 percent CI 0.3–1.7), 0.7 (95 percent CI 0.3–2.0), and 1.3 (95 percent CI 0.8–2.1), respectively. Low-dose users had a relative risk of 1.1 (95 percent CI 0.7–1.7), while those who used high doses had a relative risk of 0.9 (95 percent CI 0.2–3.7).

Nonsteroidal antiinflammatory drugs did modify the effect of calcium channel blockers. Information on the use of ethanol and tobacco as well as on past ulcer history was available from the medical record review for the cases. Use of calcium channel blockers was not significantly different among past or current smokers compared with nonsmokers (p = 0.7), users of ethanol compared with nonusers of ethanol (p = 0.5), or those with a previous history of ulcer compared with those with no ulcer history (p = 0.2).

DISCUSSION

In this retrospective cohort study, a univariate association between the use of calcium channel blockers and confirmed bleeding from peptic ulcers was explained by confounding. Even when compared with users of beta blockers, current users of calcium channel blockers were more likely to take other drugs that cause gastrointestinal bleeding and to have greater comorbidity as indicated by past use of medical care. When these factors were controlled for in a multivariate analysis, there was essentially no difference in the rates of bleeding peptic ulcers between current calcium channel and beta-blocker users.

There are two major differences between the present study and the recent report of Pahor et al. (2) from the Established Populations for Epidemiologic Studies of the Elderly (EPESE) cohort. First, our analysis is based upon cases of upper gastrointestinal bleeding related to peptic ulcers that were confirmed by medical record review. In contrast, Pahor et al. identified cases from unconfirmed Medicare claims. In conducting our study, we noted that Medicare claim diagnoses similar to those of Pahor et al. had a positive predictive value of less than 50 percent for our study outcome. While it is argued that such misclassification should weaken the association (12), this is true only if it is nondifferential. Given the higher levels of comorbidity among calcium channel blocker users, they could have had more hospitalizations that ultimately represented false positive events.

Second, information on medication use was available at only two times separated by 3 years for the EPESE cohort. The low risk (relative risk = 1.4) associated with nonsteroidal antiinflammatory drug use in that study suggests that substantial misclassification of drug exposure did occur (3). The current study relied on computerized pharmacy records to indicate drug exposure. While this methodology cannot provide information on compliance with the prescribed regimen, it is not likely to be influenced by patient characteristics or the existence of comorbid conditions.

Several chronic diseases (chronic obstructive pulmonary disease, coronary artery disease, cirrhosis, others) have been identified in some studies as potential risk factors for peptic ulcer disease (13). The importance of comorbid factors in peptic ulcer disease has been demonstrated in studies of the association between ulcer disease and nonsteroidal antiinflammatory drugs where advanced age, disability, and previous history of cardiac disease were important independent risk factors for peptic ulcer disease (14, 15). In our previous studies of peptic ulcer disease, recent hospital discharge was associated with an increased risk of admission for peptic ulcer. Whether hospitalization is a marker for general frailty or whether there are disease-specific factors that increase the risk of bleeding peptic ulcers is unclear and deserves further study.

Other differences between the studies include differences in socioeconomic status, the EPESE’s restriction to a population of hypertensives, and the inclusion in the EPESE study of lower gastrointestinal hemorrhage and bleeding related to non-ulcer conditions such as esophageal varices and gastric cancer. These factors may partially explain the difference in findings. However, our data show that, in the population studied, there was no evidence that current users of calcium channel blockers had an increased risk of bleeding peptic ulcers.

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