Antihypertensives and the Risk of Serious Hypoglycemia in Older Persons Using Insulin or Sulfonylureas

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Context.—β-Blockers and angiotensin-converting enzyme (ACE) inhibitors are effective antihypertensive agents for patients with diabetes mellitus. However, β-blockers attenuate some components of the autonomic response to hypoglycemia and could increase the risk of hypoglycemia. ACE inhibitors may increase insulin sensitivity and predispose users to hypoglycemia.

Objective.—To determine whether use of cardioselective β-blockers, nonselective β-blockers, ACE inhibitors, thiazide diuretics, calcium channel blockers, or other antihypertensive drugs alters the risk of developing serious hypoglycemia among older persons prescribed insulin or sulfonylureas.

Design.—Retrospective cohort study.

Setting.—Tennessee Medicaid Program.

Patients.—A total of 13 559 elderly (mean age, 78±7 years) Medicaid enrollees, who were prescribed insulin (n=5171, 38%) or sulfonylureas (n=8368, 62%) from 1985 through 1989. These enrollees contributed a total of 33 107 person-years of insulin or sulfonylurea use for follow-up.

Measurements.—Hospitalization, emergency department admission, or death associated with hypoglycemic symptoms and a concomitant blood glucose determination of less than 2.8 mmol/L (50 mg/dL).

Results.—We identified 598 persons with an episode of serious hypoglycemia during the study period. The rate of serious hypoglycemia was 2.01 per 100 person-years among those who were not prescribed antihypertensives. Crude rates of serious hypoglycemia were highest among users of ACE inhibitors (2.47 per 100 person-years) and lowest among users of cardioselective β-blockers (1.23 per 100 person-years). However, when we controlled for demographic characteristics and markers of comorbidity, there was no statistically significant increase or decrease in risk of serious hypoglycemia among users of any class of antihypertensive agents compared with nonusers of antihypertensive drugs. Using nonselective β-blockers as the reference group, each of these agents was associated with a lower, but not statistically significant, risk of hypoglycemia.

Conclusions.—In this population, specific antihypertensive drug therapy had little impact on the risk of hypoglycemia in older diabetic patients. Therapy should be chosen based on other considerations of safety and effectiveness.

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ALTHOUGH approximately 70% of older persons with diabetes use antihypertensives,[1] the choice of therapy to treat hypertension in this population is complicated by special considerations related to therapeutic risk. The question of increased risk of hypoglycemia is of particular concern among users of 2 potentially useful classes of antihypertensives: β-blockers and angiotensin-converting enzyme (ACE) inhibitors.

β-Blockers potentially increase the risk of serious hypoglycemia in diabetic patients because they blunt autonomic warning symptoms of hypoglycemia. Although the risk of hypoglycemia associated with β-blocker use has not been extensively studied, the fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Evaluation, and Treatment of High Blood Pressure (JNC V) states that use of β-blockers "requires special monitoring" in persons with diabetes.[2] ACE inhibitors may increase insulin sensitivity, and case reports[3,4] and 1 case-control study[5] have reported an association of hypoglycemia with ACE inhibitor use in persons with diabetes.[3,4]

Given the demonstrated clinical benefits that β-blockers and ACE inhibitors offer,[6,7] additional data regarding this important complication of hypertension treatment is needed for optimal therapeutic decision making in older persons with diabetes. We therefore performed a retrospective cohort study of elderly Tennessee Medicaid enrollees to determine whether use of any 1 of 6 classes of antihypertensives increases the risk of serious hypoglycemia in older persons prescribed either sulfonylureas or insulin.

METHODS

Source of Data

The study population was drawn from the Tennessee Medicaid program, which had an annual enrollment of approximately 85 000 persons aged 65 years or older, accounting for 15% of the state's elderly population. 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 county of residence of the enrollees. Linked Medicare-Medicaid 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*)[8] (up to 2 diagnoses in Medicaid and up to 6 in Medicare). The pharmacy file contains reimbursed prescrip-

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tions for outpatients and nursing home residents. During the study, most prescription drugs were included in the Medicaid formulary. This file identifies when the prescription was filled, the drug dispensed and its strength, 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

Eligible persons included Tennessee Medicaid enrollees aged 65 years or older with at least 1 prior year of enrollment utilization to assure a year of known medical history. Eligible persons entered the cohort on the first date of exposure to insulin or an oral hypoglycemic drug from January 1, 1985, through December 31, 1989, and were followed up until the first of the following dates: December 31, 1989, termination of Medicaid enrollment, a study event, or death.

Antihypertensive Drug Exposure

Exposure to antihypertensive drugs was determined using computerized Medicaid pharmacy claims. For this study, drug use began the day after a prescription was filled and finished at the end of the days' supply of the drug, if no refills were provided.

The 6 classes of antihypertensive drugs we studied (and the most frequently prescribed drugs in these classes) included cardioselective β-blockers (metoprolol and atenolol), nonselective β-blockers (propranolol hydrochloride and nadolol), ACE inhibitors (captopril and enalapril maleate), thiazide diuretics (hydrochlorothiazide and chlorthalidone), calcium channel blockers (nifedipine and verapamil hydrochloride), and others (clonidine hydrochloride and reserpine). Combination agents (eg, β-blockers and thiazide diuretics) were included in both categories.

Events

We used Medicaid physician, hospital, and emergency department claims to screen for the first episode of hypoglycemia after cohort entry. Eligible *ICD-9-CM* codes included hypoglycemic coma (251.0), hypoglycemia, unspecified (251.2), diabetes with other coma (250.3), functional hypoglycemia syndrome (251.1), and therapeutic misadventure (962.3). The wide range of *ICD-9-CM* codes increases the ascertainment of potential events that might otherwise be overlooked because of coding practices.

We then reviewed the relevant emergency department and hospital records to determine whether the event met our case definition for serious hypoglycemia. Events were classified as serious hypoglycemia if neuroglycopenic (eg, alteration in consciousness) or autonomic (eg, palpitations, diaphoresis) symptoms, myocardial infarction (MI), stroke, injury, or death occurred out of hospital with a concomitant blood glucose determination of less than 2.8 mmol/L (50 mg/dL). We used laboratory blood glucose determinations when available or the midpoint of the range provided by finger-stick glucose measurements.

Statistical Analysis

Incidence was determined by dividing the number of serious events by person-time of exposure. The adjusted relative risk (RR) of serious hypoglycemia associated with antihypertensive drug use was estimated using multivariate Poisson regression. Model covariates included age, sex, race, county of residence (Standard Metropolitan Statistical Area [SMSA]), hypoglycemic drug therapy (insulin, sulfonyurea, or both), and several measures of comorbidity, including nursing home residence, recent hospital discharge before event (within 1-30 days or 31-90 days), use of more than 4 categories of medications (eg, bronchodilators, anticoagulants). We dichotomized this latter variable to improve statistical efficiency, and we chose this cut point because the risk of serious hypoglycemia increased among persons who used more than 4 concomitant classes of medications. To evaluate for bias due to differences between persons with missing records and those with serious hypoglycemia, we conducted similar analyses including persons with missing records. These analyses, which classified persons with missing medical records as having serious hypoglycemia, yielded similar results. All analyses were performed using Generalized Linear Interactive Modelling (GLIM)[9] software.

RESULTS

Events

Of 1317 potential events identified using Medicaid *ICD-9-CM* codes, 981 medical records (74%) were available for review. Of these, 598 (61%) met our case definition for serious hypoglycemia and were included in the study, 88 (9%) were classified as possible hypoglycemia, and 295 (30%) were other events.

The mean (±SD) age of persons with serious hypoglycemia was 78 (±7) years. Most (82%) were women, 52% were white, and 26% were nursing home residents. The mean (±SD) plasma glucose on presentation was 1.8 (±0.6) mmol/L (33 [±10] mg/dL). Compared with persons with confirmed serious hypoglycemia, persons with missing records were younger (aged 77 [±8] years, $P=.03$) and more likely to be white (60%, $P=.03$). Otherwise, the groups were similar.

A majority presented with neuroglycopenic symptoms, including loss of consciousness (49%), lethargy (34%), syncope (10%), irrational behavior (6%), and seizures (5%). Palpitations or diaphoresis were reported by 40% of patients. A total of 26 catastrophic complications (5%), including stroke (n=7), transient ischemic attack (n=4), myocardial infarction (n=3), injury (n=10), or death (n=2), were associated with these episodes. Fever (18%) and renal insufficiency (16%), defined as admission serum urea nitrogen level greater than 14.3 mm/L (40 mg/dL) or creatinine level greater than 176.8 µmol/L (2.0 mg/dL), were common comorbidities. Patients were treated with intravenous dextrose (85%), oral carbohydrates (23%), or glucagon (1%). Although 59% of the patients improved immediately with initial treatment, 381 (64%) were admitted to a hospital, whereas 217 (36%) were discharged without inpatient evaluation.

Serious Hypoglycemia Associated With Use of Antihypertensive Agents

There were 33 107 person-years of hypoglycemic drug use, of which 20 774 (63%) were associated with sulfonylurea use and 12 333 (37%) with insulin use. The rates (per 100 person-years) of serious hypoglycemia were 1.23 (95% confidence interval [CI], 1.08-1.38) in users of sulfonylureas, 2.76 (95% CI, 2.47-3.06) among insulin users, and 3.38 (95% CI, 1.50-5.26) among users of both insulin and sulfonylureas.

There were 18 651 person-years associated with current use of 1 or more antihypertensive drugs. Single-agent use of 1 of the 6 classes of antihypertensives studied accounted for 11 170 person-years, and 7481 person-years were associated with concurrent use of more than 1 antihypertensive agent. Of 598 events that met our case definition for serious hypoglycemia, 304 (51%) occurred during current use of antihypertensives. The rate of serious hypoglycemia during current use of single-agent antihypertensive drug therapy was 1.75 (95% CI, 1.51-2.00) per 100 person-years and 1.44 (95%CI, 1.17-1.71) per 100 person-years during use of more than 1 antihypertensive drug. The rate associated with nonuse was 2.03 per 100 person-years (95% CI, 1.80-2.26 per 100 person-years). The adjusted rate of serious hypoglycemia was lower during use of antihypertensives ($P=.02$) than during nonuse person-time.

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Table 1.—Antihypertensive Drug Therapy and the Risk of Serious Hypoglycemia Among Adults Aged 65 Years or Older Prescribed Insulin or Sulfonylureas, Tennessee Medicaid Enrollees, 1985-1989*

Antihypertensive Drug Therapy	Person-Years	Hypoglycemic Events	Rate per 100 Person-Years	Relative Risk (95% CI)†
Nonusers	11 161	224	2.01	Referent
Former users	3293	70	2.12	0.96 (0.73-1.26)
Single agent				
β-Blockers, cardioselective	488	6	1.23	0.73 (0.33-1.64)
β-Blockers, nonselective	569	12	2.10	1.26 (0.71-2.26)
Angiotensin-converting enzyme inhibitor	1009	25	2.47	1.17 (0.77-1.78)
Calcium channel blocker	1505	27	1.79	0.81 (0.54-1.21)
Thiazide diuretic	5098	71	1.39	0.80 (0.61-1.05)
Other antihypertensive	2500	55	2.20	1.01 (0.75-1.37)
Multiple agents				
Thiazide and other agent	6262	83	1.32	0.80 (0.62-1.04)
Other combination	1219	25	2.05	0.99 (0.66-1.50)

*The reference group is nonusers of antihypertensive drug therapy.
†Adjusted for age, sex, race, recent hospitalization, nursing home residence, county of residence, type of hypoglycemic drug (insulin or sulfonylurea), and the use of more than 4 categories of concomitant drug therapy.

Table 2.—Relative Risk of Serious Hypoglycemia Associated With Current Use of Antihypertensive Drugs by Hypoglycemic Drug Therapy in Tennessee Medicaid Enrollees, Aged 65 Years or Older, 1985-1989*

Antihypertensive Drug Therapy	Insulin Use, Relative Risk (95% CI)† (12 333 Person-Years)	Sulfonylurea Use, Relative Risk (95% CI)† (20 774 Person-Years)
Single agent		
β-Blockers, cardioselective	0.48 (0.12-1.92)	0.86 (0.36-1.33)
β-Blockers, other	2.16 (1.16-4.02)	0.25 (0.05-1.24)
Angiotensin-converting enzyme inhibitor	1.25 (0.73-2.14)	1.05 (0.55-2.02)
Calcium channel blocker	0.61 (0.34-1.11)	1.09 (0.63-1.09)
Thiazide diuretic	0.78 (0.53-1.14)	0.80 (0.54-1.18)
Other antihypertensive	1.09 (0.74-1.59)	0.92 (0.57-1.50)
Multiple agents		
Thiazide and other agent	0.80 (0.56-1.15)	0.79 (0.54-1.16)
Other combination	0.91 (0.53-1.60)	1.09 (0.58-2.03)

*Current use of antihypertensive drugs compared with nonuse of antihypertensive drugs.
†Adjusted for age, sex, race, recent hospitalization, nursing home residence, county of residence, and the use of more than 4 categories of concomitant drug therapy.

Table 3.—Rates and Adjusted Relative Risk of Serious Hypoglycemia Among Tennessee Medicaid Enrollees Aged 65 Years and Older Prescribed Single-Agent Antihypertensive Drug Therapy, 1985-1989*

Antihypertensive Drug Therapy	Person-Years	Hypoglycemic Events	Rate, Per 100 Person-Years	Relative Risk (95% CI)†
β-Blockers, nonselective	569	12	2.10	Referent
β-Blockers, cardioselective	488	6	1.23	0.58 (0.22-1.54)
Angiotensin-converting enzyme inhibitor	1009	25	2.47	0.93 (0.46-1.85)
Calcium channel blocker	1505	27	1.79	0.64 (0.32-1.27)
Thiazide diuretic	5098	71	1.39	0.63 (0.34-1.16)
Other antihypertensive	2500	55	2.20	0.80 (0.43-1.51)

*The reference group consists of individuals using nonselective β-blockers.
†Adjusted for age, sex, race, recent hospitalization, nursing home residence, county of residence, type of hypoglycemic drug (insulin or sulfonylurea), and the use of more than 4 categories of concomitant drug therapy.

Among users of antihypertensive drugs, the rate of serious hypoglycemia ranged from 2.47 (ACE inhibitors) to 1.23 (cardioselective β-blockers) events per 100 person-years. Compared with nonusers of hypertensive drugs, there was a trend toward decreased risk of serious hypoglycemia among users of thiazide diuretics alone ($P=.11$) or in combination with other antihypertensive drugs ($P=.09$), but in no therapeutic category did the 95% CI exclude 1 (Table 1).

Among users of insulin, the use of nonselective β-blockers was associated with a significant ($P=.01$) 2-fold increased risk of serious hypoglycemia. No other use of hypertensive medication achieved statistical significance in either insulin users or users of sulfonylureas (Table 2).

Because of our a priori hypothesis that users of nonselective β-blockers would be at the highest risk for serious hypoglycemia, we compared the risk of serious hypoglycemia among single-agent users of 5 classes of antihypertensives with that among single-agent users of nonselective β-blockers. The adjusted RR ranged from 0.58 among users of cardioselective β-blockers to 0.93 among users of ACE inhibitors. Although each of these agents was associated with a lower risk of hypoglycemia than nonselective β-blockers, in none of these agents did the 95% CI exclude 1 (Table 3).

COMMENT

In this large cohort of elderly Tennessee Medicaid enrollees, the RR of serious hypoglycemia among users of antihypertensive drugs ranged from 1.26 (nonselective β-blockers) to 0.80 (thiazide diuretics) compared with that in persons not prescribed antihypertensive drugs. Compared with users of nonselective β-blockers, the adjusted RRs of serious hypoglycemia ranged from 0.58 (cardioselective β-blockers) to 0.93 (ACE inhibitors). Although nonselective β-blockers were associated with the highest rate of hypoglycemia, none of the findings was statistically significant. In addition, results for nonselective β-blockers were inconsistent, such that an elevated risk of hypoglycemia was observed only among insulin users. Although we cannot rule out a small increased risk associated with use of nonselective β-blockers, our findings coupled with those of smaller studies[5,10] provide substantial evidence that cardioselective β-blockers do not increase the risk of serious hypoglycemia in persons with diabetes. In fact, when compared with users of nonselective β-blockers, the risk of serious hypoglycemia among users of cardioselective β-blockers in our study was lower than any other class of antihypertensive drugs.

We did not find an increased risk of hypoglycemia among persons using ACE inhibitors. This is in contrast to the findings of Herings and colleagues.[5] They identified 98 persons using hypoglycemic drugs hospitalized with a primary diagnosis of hypoglycemia and 654 population-based controls from a computer-linked pharmacy and medical records system. Current use of ACE inhibitors was associated with a nearly 3-fold increased risk of hypoglycemia (odds ratio, 2.8 [95% CI, 1.4-5.7]). The reason for this discrepancy is unknown; however, because 95% CIs of both studies overlap and are compatible with a 40% to 70% increase in risk of hypoglycemia associated with use of ACE inhibitors, further studies are needed to better estimate the risk of hypoglycemia associated with ACE inhibitor use in persons using hypoglycemic drugs.

Compared with nonusers, users of thiazide diuretics had a lower (but nonsignificant) likelihood of hypoglycemia, when used as a single agent or in combination with other antihypertensives. The relationship between thiazide diuretics and impaired glucose control among persons with diabetes is controversial,[11,12] and whether thiazides were associated with

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a decreased risk of hypoglycemia by increasing glucose levels is speculative and would be better addressed in a prospective study.

Our study has several important limitations. First, our sample size limited our ability to detect small RRs. Detectable (α [2-sided]=.05 and β=.20) RRs were 2.1 for cardioselective β-blockers, 1.95 for nonselective β-blockers, 1.71 for ACE inhibitors, and 1.4 for thiazide diuretics. Second, nearly one fourth of our medical records were unavailable for review; thus, ascertainment of serious hypoglycemic events was incomplete. While this may result in a modest underestimation of our rate of serious hypoglycemia, analysis that included persons with missing medical records as having serious hypoglycemia yielded similar results. Third, a biased underestimate of risk could occur if β-blockers were avoided in patients most prone to hypoglycemia. We attempted to minimize "confounding by contraindication" by excluding person-time after the first potential event, which might reflect changes in antihypertensive therapy in response to an episode of hypoglycemia. We also controlled for other comorbidities that predispose individuals to serious hypoglycemic events. Fourth, because these data were rarely present in the hospital and emergency department records, we could not adequately control for several potentially important confounders, including desired degree of diabetes control, duration of diabetes, weight, and renal or hepatic function. However, it is unlikely that these factors varied systematically by antihypertensive drug use. Finally, our study concluded in 1989 and, thus, does not take into consideration recent secular trends in diabetes management, which may have resulted in more rigorous attempts to improve glycemic control. Because of these limitations, further observational and prospective studies should be performed to confirm our findings.

A long-held belief is that the use of β-adrenoreceptor blockade blunts hypoglycemic awareness, thus increasing the risk of neuroglycopenia. However, although β-blockade attenuates heart rate and blood pressure responses in hypoglycemic subjects, other warning symptoms such as diaphoresis are unaffected[13] or accentuated.[14] This may explain the finding that awareness of hypoglycemia is not impaired in diabetic patients with autonomic neuropathy.[15,16]

β-Blockers offer several advantages in the treatment of hypertension or heart disease among persons with diabetes. As reviewed by Tse and Kendall,[7] the cardioprotective effects of β-blockers following myocardial infarction in persons with diabetes equal or exceed those in nondiabetic subjects.[17-23] Despite compelling evidence of therapeutic efficacy, these agents are often not recommended for use in persons with medically treated diabetes because of the potential to increase hypoglycemic risk.[2,11,12,24,25] In the population we studied, specific antihypertensive drug therapy had little impact on the risk of hypoglycemia in older persons using hypoglycemic drugs. The evidence to support the commonly held belief that β-blockers increase hypoglycemic risk is weak, and data linking cardioselective β-blockers to increased risk of hypoglycemia in persons with diabetes are absent. Thus, drug therapy for hypertension in persons with diabetes should be chosen based on other considerations of safety and effectiveness.

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