Drug-Drug Interactions Among Elderly Patients Hospitalized for Drug Toxicity

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Context Drug-drug interactions are a preventable cause of morbidity and mortality, yet their consequences in the community are not well characterized.

Objective To determine whether elderly patients admitted to hospital with specific drug toxicities were likely to have been prescribed an interacting drug in the week prior to admission.

Design Three population-based, nested case-control studies.

Setting Ontario, Canada, from January 1, 1994, to December 31, 2000.

Patients All Ontario residents aged 66 years or older treated with glyburide, digoxin, or an angiotensin-converting enzyme (ACE) inhibitor. Case patients were those admitted to hospital for drug-related toxicity. Prescription records of cases were compared with those of controls (matched on age, sex, use of the same medication, and presence or absence of renal disease) for receipt of interacting medications (co-trimoxazole with glyburide, clarithromycin with digoxin, and potassium-sparing diuretics with ACE inhibitors).

Main Outcome Measure Odds ratio for association between hospital admission for drug toxicity (hypoglycemia, digoxin toxicity, or hyperkalemia, respectively) and use of an interacting medication in the preceding week, adjusted for diagnoses, receipt of other medications, the number of prescription drugs, and the number of hospital admissions in the year preceding the index date.

Results During the 7-year study period, 909 elderly patients receiving glyburide were admitted with a diagnosis of hypoglycemia. In the primary analysis, those patients admitted for hypoglycemia were more than 6 times as likely to have been treated with co-trimoxazole in the previous week (adjusted odds ratio, 6.6; 95% confidence interval, 4.5-9.7). Patients admitted with digoxin toxicity (n=1051) were about 12 times more likely to have been treated with clarithromycin (adjusted odds ratio, 11.7; 95% confidence interval, 7.5-18.2) in the previous week, and patients treated with ACE inhibitors admitted with a diagnosis of hyperkalemia (n=523) were about 20 times more likely to have been treated with a potassium-sparing diuretic (adjusted odds ratio, 20.3; 95% confidence interval, 13.4-30.7) in the previous week. No increased risk of drug toxicity was found for drugs with similar indications but no known interactions (amoxicillin, cefuroxime, and indapamide, respectively).

Conclusions Many hospital admissions of elderly patients for drug toxicity occur after administration of a drug known to cause drug-drug interactions. Many of these interactions could have been avoided.

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Adverse drug events affect millions of patients each year and are responsible for up to 5% of hospital admissions.[1,2] They also pose an enormous financial burden, with an estimated cost of more than $16 000 per hospitalization.[3] While some adverse drug events are unpredictable (such as anaphylaxis from an unrecognized allergy), many others can be anticipated and prevented.

Drug-drug interactions are a particularly important type of adverse drug event because they are often predictable based on previous reports, clinical studies, and an understanding of pharmacologic principles. Some adverse drug events have life-threatening consequences and may prompt the removal of popular medications from the marketplace.[4-10] Such drastic measures are probably justifiable because clinicians are often unaware of serious drug-drug interactions.[11-15] Moreover, the computer systems intended to help avert dangerous drug combinations fail to detect up to a third of drug-drug interactions, while frequently alerting pharmacists to trivial or nonspecific interactions.[14,16,17]

Little information is available about the epidemiology of drug-drug interactions in clinical practice, and most of the evidence is derived from case reports, volunteer studies, or investigations of potential drug-drug interactions in hospitalized patients.[18-23] No studies to date have examined clinical outcomes of

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drug-drug interactions in a population-based fashion. In this study, we used population-based health care records to explore the association between adverse clinical outcomes and avoidable drug-drug interactions in elderly patients. We focused on 3 drug-drug interactions that involve commonly used medications and that produce specific toxic effects identifiable with administrative data. Patients with diabetes treated with sulfonylureas, such as glyburide, are at risk for hypoglycemia when taking sulfonamide antibiotics, in part because these drugs inhibit glyburide's metabolism by the cytochrome P450 2C9 (CYP 2C9) enzyme system.[24-30] Digoxin toxicity can easily develop in patients simultaneously treated with clarithromycin because the latter inhibits P-glycoprotein,[31] a multidrug efflux pump that promotes the renal clearance of digoxin.[32-35] Hyperkalemia is common among patients treated with angiotensin-converting enzyme (ACE) inhibitors,[36,37] and the concomitant use of potassium-sparing diuretics can precipitate life-threatening hyperkalemia.[38,39]

METHODS

Setting and Design

We conducted 3 separate population-based, nested case-control studies by linking multiple health care databases over 7 years (January 1, 1994, to December 31, 2000) in Ontario, Canada. Ontario is Canada's most populous province, with a population of approximately 12 million of whom approximately 1.5 million are aged 65 years or older.[40] These elderly patients have universal access to hospital care, physicians' services, and prescription drug coverage, and they can be analyzed in an anonymous fashion using encrypted individual health card numbers. This research project was approved by the ethics review board of Sunnybrook and Women's College Health Sciences Centre, Toronto.

Data Sources

We examined the computerized prescription records of the Ontario Drug Benefit Program, which records prescription drugs dispensed to all Ontario residents aged 65 years or older. Hospitalization records were obtained from the Canadian Institute for Health Information Discharge Abstract Database, which contains a detailed record of all hospital admissions, including diagnostic and procedural information. The Ontario Health Insurance Plan provided information on physician claims for inpatient and outpatient services, and the Ontario Registered Persons Database contained basic demographic information for each Ontario resident aged 65 years or older. These databases have been used previously to study other population-based health outcomes.[41-43] Because we used a deterministic rather than a probabilistic matching process, the linkage rate among databases was 100%.

Individual Observation Period

We studied a period of continuous use of each study medication (glyburide, digoxin, or ACE inhibitor) for every patient beginning with the first prescription following his or her 66th birthday. The observation period ended with either hospital admission for drug toxicity, the end of the study period, death, or discontinuation of the study medication (whichever occurred first). Patients were considered to have discontinued the study medication if more than 6 months elapsed between prescriptions for the drug; in such cases, we extended the observation period to 2 months after the last filled prescription to include admissions for drug toxicity that may have prompted cessation of therapy. A similar method has been used previously to define courses of continuous drug utilization.[43-45] For cases, the index date was the date of hospital admission; the same date was used as the index date for the corresponding controls.

Case Patients

Within the cohort of continuous users of glyburide, we defined case patients as those admitted to hospital with a most responsible diagnosis (defined as the principal diagnosis contributing to the greatest extent to hospital stay[46]) of hypoglycemia (*International Classification of Diseases, Ninth Revision [ICD-9]*[47] codes 251.0 or 251.2). Within the group of digoxin users, cases were those admitted to hospital with a most responsible diagnosis of digoxin toxicity (*ICD-9* code 972.1). Within the group of patients receiving an ACE inhibitor, cases were those admitted to hospital with a most responsible diagnosis of hyperkalemia (*ICD-9* code 276.7). The date of hospital admission served as the index date for all analyses. Only the first adverse event was considered for patients admitted more than once for the same diagnosis.

Control Patients

We selected 50 controls for each case, matching on age, sex, continuous use of the same long-term medication, and presence or absence of renal disease as determined by detailed examination of all physician claims, hospital admissions, and inpatient or outpatient dialysis treatments in the preceding year. When numerous potential controls existed for a case, 50 were randomly chosen for analysis. When fewer than 50 potential controls were available, we analyzed only those available controls and maintained the matching process. Because each interaction was studied independent of the others, patients could serve as case or control subjects in any of the interaction studies, depending on their medication use and history of hospitalization. Overall, 95% of patients were matched to 50 controls: glyburide, 840 (92%) of 909 cases; digoxin, 1017 (97%) of 1051; and ACE inhibitors, 506 (97%) of 523.

Exposure to Interacting Medications

In the glyburide analysis, *exposure* was defined as any prescription for cotrimoxazole. To test the specificity of our findings, we also examined prescriptions for amoxicillin, another antibiotic that is widely used by elderly patients but is not known to potentiate the effect of sulfonylureas. In the digoxin analysis, we identified prescriptions for

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clarithromycin, using cefuroxime as a comparable drug without no known interaction with digoxin. In the ACE inhibitor analysis, we identified prescriptions for single-agent potassium-sparing diuretics (amiloride, triamterene, or spironolactone), and indapamide was used for comparison.

Statistical Analysis

The primary analysis considered prescriptions in the week prior to the index hospital admission for drug toxicity, and the secondary analyses considered prescriptions within 2 and 3 weeks prior to the index hospital admission for drug toxicity. In each analysis, conditional logistic regression was used to estimate the odds ratio (OR) and 95% confidence intervals (CIs) for the association between medication use and hospital admission for drug toxicity. To estimate the proportion of admissions that could be averted by avoiding each interaction, attributable fractions were calculated from the 1-week analyses using standard methods in which the attributable fraction equals the OR minus 1, divided by the OR, and then multiplied by the proportion of patients exposed to the interacting medication of interest.[46,48-50]

We performed multivariate analysis adjusting for diagnoses and receipt of other medications that could potentially influence these outcomes, as well as for the number of prescription drugs[51] and hospital admissions in the year before the index date. Finally, patients with a previous history of these adverse outcomes may have more subtle reasons to experience a recurrence, so we also adjusted for any history of hospitalization for the diagnosis of interest in the 3 years prior to cohort entry. To avoid overfitting the model, drugs that could have confounded the model were grouped by mechanism rather than inserted individually (TABLE 1). The model for glyburide had 9 covariates, digoxin had 6 covariates, and ACE inhibitors had 8 covariates. All analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC).

Table 1. Covariates Included in the Multivariate Models

Outcome (Drug)	Potential Predictor	Specific Medications or Conditions*
Hypoglycemia (glyburide)	Other oral hypoglycemics	Other oral hypoglycemic agents
	Insulin preparations	Insulin preparations
	Agents potentially causing hyperglycemia	Thiazide diuretics, β-adrenergic antagonists, corticosteroids
	Potential CYP 2C9 inducers	Rifampin, barbiturates, dexamethasone
	Potential CYP 2C9 inhibitors	Cimetidine and others†
	Miscellaneous interacting medications	Verapamil
	Previous hospital admission for hypoglycemia‡	
Digoxin toxicity (digoxin)	Other P-glycoprotein inhibitors	Verapamil and others§
	Agents lowering digoxin levels	Cholestyramine
	Agents causing hypokalemia	Thiazide and loop diuretics
	Previous hospital admission for digoxin toxicity‡	
Hyperkalemia (ACE inhibitors)	Potassium supplements	Potassium chloride or gluconate
	Inhibitors of kaliuresis	Trimethoprim and others‖
	Promoters of kaliuresis	Hydrochlorothiazide, chlorthalidone, loop diuretics
	Agents potentially altering transmembrane potassium distribution	β-Adrenergic antagonists
	Diabetes mellitus	Oral hypoglycemics or insulin¶
	Previous hospital admission for hyperkalemia‡	
All outcomes	Number of prescription drugs dispensed in preceding year	
	Number of hospital admissions in preceding year	

Abbreviations: ACE, angiotensin-converting enzyme; CYP, cytochrome P.
*In the primary analysis, adjustment is made for use of any of these medications in 90 days preceding the index date unless otherwise noted. Each predictor category comprises a single term in the multivariate model.
†Other medications include amiodarone, disulfiram, fluconazole, fluvastatin, fluvoxamine, isoniazid, paroxetine, sertraline, and zafirlukast.
‡Hospital admission for the drug-related toxicity of interest in 3 years preceding cohort entry.
§Other medications include amiodarone, cyclosporine, diltiazem, ketoconazole, nifedipine, propafenone, quinidine, quinine, and tamoxifen.
‖Medications include combinations of amiloride, triamterene, or spironolactone with a thiazide diuretic.
¶Any prescription for oral hypoglycemic agents or insulin in the 3 years preceding the index date.

Sensitivity Analyses

We repeated our analyses with a variety of modifications to assess the robustness of our findings. For patients who appeared to discontinue their long-term medication (glyburide, digoxin, or ACE inhibitor) by virtue of a lapse between refills of more than 6 months, we reduced this period to 3 months, and we altered the extension to the observation period following the final prescription from 2 months to 1 month and then to 3 months. For each of these sensitivity analyses we repeated the entire analysis including reselection of cases and controls. We also repeated the multivariate analysis, adjusting for exposure to other interacting medications within 2 weeks, 4 weeks, 6 weeks, and 8 weeks of the index date. We also performed a supplementary analysis examining the relationship between outcomes and interacting drug use among patients who started their long-term medication within 30 days of the index date. As a final test of robustness, we repeated our analysis using nonparametric bootstrap methods[52] in which univariate and multivariate analyses were repeated 1000 times using a 4:1 matching process with random selection of different control patients on each iteration.

RESULTS

Primary Analyses

We identified 179 986 elderly patients treated with glyburide continuously for a total of 431 662 patient-years of therapy.

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Table 2. Characteristics of Cases and Controls

	Glyburide With Co-trimoxazole		Digoxin With Clarithromycin		ACE Inhibitors With K^+-Sparing Diuretics	
	Cases (n = 909)	Controls (n = 43 766)	Cases (n = 1051)	Controls (n = 51 896)	Cases (n = 523)	Controls (n = 25 807)
Age, median (IQR), y	78.6 (72.8-83.9)	78.2 (72.7-83.3)	80.6 (75.4-85.8)	80.5 (75.3-85.7)	78.4 (72.3-84.5)	78.2 (72.8-84.3)
Years using index drug, median (IQR)	1.2 (0.4-2.7)	1.4 (0.6-2.9)	1.1 (0.2-3.0)	1.9 (0.7-3.4)	1.5 (0.6-3.2)	1.7 (0.8-3.4)
Female, No. (%)	500 (55)	23 910 (55)	686 (65)	34 121 (66)	272 (52)	13 538 (52)
Residence in long-term care facility, No. (%)	92 (10)	2925 (7)	57 (5)	5458 (11)	58 (11)	1789 (7)
No. of hospital admissions in previous year, median (IQR)	1 (0-2)	0 (0-0)	1 (0-2)	0 (0-1)	1 (0-2)	0 (0-1)
No. of prescription drugs in previous year, median (IQR)	14 (10-19)	10 (7-15)	16 (11-21)	12 (8-17)	16 (12-22)	11 (7-16)
Renal disease in preceding year, No. (%)	226 (24.9)	10 235 (23.4)	322 (30.6)	15 605 (30.1)	308 (58.9)	15 057 (58.3)
Drug first dispensed within 30 days, No. (%)	92 (10.1)	2347 (5.4)	198 (18.8)	1772 (3.4)	41 (7.8)	958 (3.7)
Medication use in preceding year, No. (%)						
ACE inhibitors	448 (49)	15 886 (36)	659 (63)	23 983 (46)	523 (100)	25 807(100)
Antidiabetic agents	909 (100)	43 766 (100)	238 (23)	10 398 (20)	209 (40)	6089 (24)
Aspirin	318 (35)	13 574 (31)	409 (39)	16 503 (32)	211 (40)	8701 (34)
β-Adrenergic antagonists	178 (20)	8897 (20)	257 (24)	10 989 (21)	176 (34)	6235 (24)
Calcium antagonists	328 (36)	14 133 (32)	429 (41)	16 291 (31)	226 (43)	8741 (34)
Digoxin	255 (28)	8298 (19)	1051 (100)	51 896 (100)	224 (43)	6077 (24)
Diuretics	479 (53)	14 644 (33)	848 (81)	30 743 (59)	399 (76)	13 752 (53)
Oral corticosteroids	79 (9)	2134 (5)	146 (14)	4042 (8)	57 (11)	1838 (7)
NSAIDs	510 (56)	21 636 (49)	558 (53)	23 941 (46)	295 (56)	12 945 (50)
Oral anticoagulants	100 (11)	3350 (8)	350 (33)	15 686 (30)	96 (18)	3265 (13)

Abbreviations: ACE, angiotensin-converting enzyme; IQR, interquartile range; K^+, potassium; NSAIDs, nonsteroidal anti-inflammatory drugs.

The median (interquartile range [IQR]) age was 71.6 (67.2-77.3) (7.2) years and 51% were women (TABLE 2). A total of 909 patients were admitted to hospital with a most responsible diagnosis of hypoglycemia. These patients had been treated with glyburide for a median (IQR) of 1.2 (0.4-2.7) years. The median (IQR) length of hospital stay for hypoglycemia was 4 (2-7) days and 12 patients (1.3%) died while in the hospital.

Compared with controls with no diagnosis of hypoglycemia before adjusting for other factors, cases were about 8 times more likely to have received a prescription for co-trimoxazole in the week prior to admission (OR, 8.5; 95% CI, 5.8-12.4) (TABLE 3). As expected, we found no significant association between hypoglycemia and use of amoxicillin in the preceding week in patients receiving glyburide (OR, 1.8; 95% CI, 1.0-3.5). Multivariate adjustment for use of insulin, other hypoglycemic agents, and additional factors (Table 1) that might have affected glycemic control yielded similar findings (Table 3). Overall, we estimate that at least 3.3% of the hospital admissions for hypoglycemia in elderly patients receiving glyburide could have been prevented if the simultaneous use of co-trimoxazole had been avoided.

Table 3. Association Between Hospital Admission for Hypoglycemia and Use of Co-trimoxazole in Patients Receiving Glyburide

	No. (%) Exposed			
	Cases (n = 909)	Controls (n = 43 766)	Univariate Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*
Hospitalization Within 1 Week of Exposure to Second Drug				
Co-trimoxazole	35 (3.9)	189 (0.4)	8.5 (5.8-12.4)	6.6 (4.5-9.7)
Amoxicillin†	10 (1.1)	246 (0.6)	1.8 (1.0-3.5)	1.5 (0.8-2.9)
Hospitalization Within 2 Weeks of Exposure to Second Drug				
Co-trimoxazole	49 (5.4)	319 (0.7)	7.3 (5.4-10.0)	5.7 (4.1-7.9)
Amoxicillin†	13 (1.4)	433 (1.0)	1.4 (0.8-2.5)	1.1 (0.6-2.0)
Hospitalization Within 3 Weeks of Exposure to Second Drug				
Co-trimoxazole	56 (6.2)	447 (1.0)	6.1 (4.6-8.1)	4.9 (3.6-6.6)
Amoxicillin†	19 (2.1)	611 (1.4)	1.5 (0.9-2.3)	1.2 (0.8-1.9)

Abbreviation: CI, confidence interval.
*Multivariate analysis adjusted for factors in Table 1.
†Comparable noninteracting drug for comparison.

We identified 231 257 patients receiving digoxin for a total of 513 036 patient-years of therapy. The median (IQR) age was 77.4 (71.5-83.4) years and 54% were women. A total of 1051 patients were admitted to hospital for digoxin toxicity. These patients had been treated with digoxin for a median (IQR) of 1.1 (0.2-3.0) years (Table 2). The median (IQR) length of hospital stay for digoxin toxicity was 5 (3-8) days, and 33 patients (3%) died while in the hospital.

Compared with controls without digoxin toxicity, before adjustment for confounding factors, cases were about 13 times more likely to have received a prescription for clarithromycin in the week prior to hospital admission (OR, 13.6; 95% CI, 8.8-20.8) (TABLE 4). We

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found no significant association between digoxin toxicity and exposure to cefuroxime in the preceding week (OR, 2.0; 95% CI, 0.6-6.4). Multivariate adjustment for use of amiodarone, verapamil, and other factors (Table 1) that may have influenced digoxin levels yielded similar results (Table 4). Overall, we estimate that at least 2.3% of the hospital admissions of elderly patients for digoxin toxicity could have been prevented if the simultaneous use of clarithromycin had been avoided.

We analyzed 622 285 patients receiving ACE inhibitors for a total of 1 222 093 patient-years of therapy. The median (IQR) age was 73.2 (68.3-79.2) years and 56% were women. Overall, 523 of these patients were subsequently admitted to the hospital because of hyperkalemia. These patients had been treated with ACE inhibitors for a median (IQR) of 1.5 (0.6-3.2) years (Table 2). The median (IQR) length of hospitalization was 3 (2-6) days, and 21 patients (4%) died while in the hospital.

Compared with controls receiving ACE inhibitors who were not admitted for hyperkalemia, before adjusting for confounding factors, case patients were about 27 times more likely to have received a prescription for a potassium-sparing diuretic in the week before hospital admission (OR, 27.2; 95% CI, 18.6-39.9) (TABLE 5). As expected, we found no association between hospital admission for hyperkalemia and use of indapamide among patients receiving ACE inhibitors. Multivariate adjustment for previous admissions for hyperkalemia and other factors (Table 1) that may have influenced potassium levels yielded consistent findings (Table 5). Overall, we estimate that at least 7.8% of the hospital admissions for hyperkalemia in elderly patients receiving ACE inhibitors could have been prevented if the simultaneous use of potassium-sparing diuretics had been avoided.

For every drug-drug interaction, sensitivity analyses using various definitions of the discontinuation date, individual observation period, and covariate exposure interval, as well as analyses using nonparametric bootstrap techniques yielded uniformly consistent results. In all cases, the point estimate from the bootstrap lies within the 95% CIs of the standard analysis.

When we considered only those cases and controls whose index date occurred within 30 days of commencing therapy with either glyburide, digoxin, or an ACE inhibitor, we found similar results. Among cases (n=92) who had recently started glyburide therapy, 7 (7.6%) also had received co-trimoxazole in the preceding week, while among newly treated controls (n=2347), only 55 (2.3%) received co-trimoxazole. Among cases (n=198) who had recently started digoxin, 11 (5.6%) also had been exposed to clarithromycin in the preceding week, while among newly treated controls (n=1772), only 20 (1.1%) had received clarithromycin. Finally, among cases (n=41) who had recently started an ACE inhibitor, 10 (24.4%) also had received a potassium-sparing diuretic in the preceding week, while among newly treated controls (n=958), only 12 (1.3%) received a potassium-sparing diuretic. Prescription rates for comparison noninteracting drugs (amoxicillin, cefuroxime, and indapamide) were not significantly different between cases and controls in any analysis.

Table 4. Association Between Hospital Admission for Digoxin Toxicity and Use of Clarithromycin in Patients Receiving Digoxin

	No. (%) Exposed			
	Cases (n = 1051)	Controls (n = 51 896)	Univariate Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)
Hospitalization Within 1 Week of Exposure to Second Drug				
Clarithromycin	27 (2.6)	101 (0.2)	13.6 (8.8-20.8)	11.7 (7.5-18.2)
Cefuroxime†	3 (0.3)	68 (0.1)	2.0 (0.6-6.4)	1.3 (0.4-4.1)
Hospitalization Within 2 Weeks of Exposure to Second Drug				
Clarithromycin	42 (4.0)	195 (0.4)	11.1 (7.9-15.6)	9.2 (6.5-13.1)
Cefuroxime†	3 (0.3)	123 (0.2)	1.1 (0.4-3.6)	0.8 (0.2-2.4)
Hospitalization Within 3 Weeks of Exposure to Second Drug				
Clarithromycin	55 (5.2)	274 (0.5)	10.6 (7.9-14.3)	8.5 (6.2-11.6)
Cefuroxime†	5 (0.5)	173 (0.3)	1.4 (0.6-3.4)	0.9 (0.4-2.3)

Abbreviation: CI, confidence interval.
*Multivariate analysis adjusted for factors in Table 1.
†Comparable noninteracting drug for comparison.

Table 5. Association Between Hospital Admission for Hyperkalemia and Use of Potassium-Sparing Diuretics* in Patients Receiving Angiotensin-Converting Enzyme Inhibitors

	No. (%) Exposed			
	Cases (n = 523)	Controls (n = 25 807)	Univariate Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)†
Hospitalization Within 1 Week of Exposure to Second Drug				
K^+-sparing diuretics	43 (8.2)	87 (0.3)	27.2 (18.6-39.9)	20.3 (13.4-30.7)
Indapamide‡	3 (0.6)	117 (0.4)	1.3 (0.4-4.0)	2.6 (0.8-8.5)
Hospitalization Within 2 Weeks of Exposure to Second Drug				
K^+-sparing diuretics	77 (14.7)	145 (0.6)	31.1 (23.1-42.0)	24.0 (17.4-33.1)
Indapamide‡	5 (1.0)	225 (0.9)	1.1 (0.5-2.7)	1.7 (0.6-4.5)
Hospitalization Within 3 Weeks of Exposure to Second Drug				
K^+-sparing diuretics	116 (22.2)	201 (0.8)	39.5 (30.4-51.5)	31.9 (23.9-42.6)
Indapamide‡	5 (1.0)	330 (1.3)	0.8 (0.3-1.8)	1.2 (0.5-3.2)

Abbreviations: CI, confidence interval; K^+, potassium.
*Single-agent potassium-sparing diuretics include amiloride, triamterene, and spironolactone.
†Multivariate analysis adjusted for factors in Table 1.
‡Comparable noninteracting drug for comparison.

Use of Medications After Hospital Discharge

Hospital admission for drug toxicity appeared to influence subsequent use of glyburide, digoxin, and ACE inhibi-

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tors. Many case patients did not resume these medications after hospital discharge, as evidenced by no further prescriptions in the ensuing 6 months. Of the 897 patients who were admitted to hospital for hypoglycemia and survived, 374 (42%) had no more prescriptions for glyburide during the next 6 months. Of the 1018 patients who were admitted to hospital for digoxin toxicity and survived, 344 (34%) had no more prescriptions for digoxin during the next 6 months. Of 502 patients who were admitted to hospital for hyperkalemia and survived, 212 (42%) had no more prescriptions for an ACE inhibitor during the next 6 months.

COMMENT

Using population-based health services research methods, we identified many avoidable hospital admissions for drug-related toxicity within a week following predictable drug-drug interactions in elderly patients. To avoid ambiguity, we studied only those hospital admissions directly related to drug toxicity, purposefully excluding more than 6000 other hospital admissions in which hypoglycemia, digoxin toxicity, or hyperkalemia were secondary diagnoses contributing to hospitalization and still possibly the result of a drug-drug interaction. The reliable linkage of prescription records to adverse health outcomes is impossible for countless other interactions.[19] As a result, our findings reflect only a small fraction of the problem of drug-drug interactions in elderly patients, a group that is particularly susceptible by virtue of polypharmacy, comorbid illness, and treatment by multiple physicians.[53-56]

Many of the hospitalizations we identified could probably have been avoided with closer patient monitoring or the use of alternative medications. However, it is unrealistic to expect clinicians to memorize the thousands of drug-drug interactions and their clinical significance,[19] especially considering the rate of introduction of new drugs and the burgeoning appreciation of the importance of pharmacogenetics.[57-59] Reliable, regularly updated decision support systems and information technology are necessary to help avert dangerous drug combinations. Computers are present in every modern dispensary and can reduce the likelihood of some drug-drug interactions.[17,23] However, computers sometimes fail at this important task because of a lack of regular updates, or because frequent warnings of a trivial nature fatigue the operators and lead them to override more significant ones.[14,20,22,60]

Several limitations of our study merit emphasis. We used administrative data, we have no direct measure of drug levels, renal function, or adherence to medications, and the accuracy of hospital discharge coding for some outcomes is unknown. However, any random miscoding tends to attenuate our findings. Patients exposed to interacting medications may have been sicker and hence more likely to be diagnosed with toxicity while seeking medical care; however, our finding that comparable medications (amoxicillin, cefuroxime, and indapamide) were not associated with adverse health outcomes makes confounding by illness much less plausible. In addition, the association with interacting drugs remained strong after controlling for the number of hospital admissions and for the number of prescription drugs dispensed in the preceding year, a validated measure of comorbidity.[52] Of note, the drug combinations we studied may sometimes be appropriate (eg, spironolactone with an ACE inhibitor).[61] In such instances, closer monitoring of the patient may be preferable to avoiding the drug combination.

The attributable fractions we calculate for each drug-drug interaction are conservative estimates that consider only those prescriptions dispensed within 7 days of hospital admission; they are not applicable to other manifestations of drug toxicity. Finally, ascertainment bias may have led some physicians to diagnose drug toxicity because they were aware of the predisposing drug-drug interaction. However, this is an unlikely explanation for our findings because the outcomes we studied (hypoglycemia, digoxin toxicity, and hyperkalemia) are all easily diagnosed using standard laboratory tests. Furthermore, the high rate of discontinuation of glyburide, digoxin, and ACE inhibitors after hospital discharge may reflect unawareness that drug toxicity might have been precipitated by a reversible insult, such as an interacting medication.

This is the first study published to date to use population-based data to study specific adverse health outcomes following the coprescription of drugs with known interactions. The study represents an advance over voluntary reporting of adverse drug events, a process which is important but vulnerable to underreporting.[62-64] Population-based methods may serve as a powerful tool for investigators wishing to explore the epidemiology of other drug-drug interactions. Our findings emphasize the potential dangers of commonly used medications and highlight the need for more timely collaboration between the scientists who study drug-drug interactions and those who design the computer systems intended to prevent them.[65] Physicians should be aware of these drug-drug interactions and consider prescribing alternative agents when appropriate. Alternatively, they should consider dose adjustments and monitor patients closely for evidence of drug toxicity.

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Analysis and interpretation of the data: Juurlink, Mamdani, Kopp, Laupacis, Redelmeier.
Drafting of the manuscript: Juurlink, Redelmeier.
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