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RESEARCH

Co-trimoxazole and sudden death in patients receiving inhibitors of renin-angiotensin system: population based study

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Abstract

Objective To determine whether the prescription of co-trimoxazole with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker is associated with sudden death.

Design Population based nested case-control study.

Setting Ontario, Canada, from 1 April 1994 to 1 January 2012.

Participants Ontario residents aged 66 years or older treated with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker. Cases were those who died suddenly shortly after receiving an outpatient prescription for one of co-trimoxazole, amoxicillin, ciprofloxacin, norfloxacin, or nitrofurantoin. Each case was matched with up to four controls on age, sex, chronic kidney disease, and diabetes.

Main outcome measure Odds ratio for the association between sudden death and exposure to each antibiotic relative to amoxicillin, after adjustment for predictors of sudden death according to a disease risk index.

Results Of 39 879 sudden deaths, 1027 occurred within seven days of exposure to an antibiotic and were matched to 3733 controls. Relative to amoxicillin, co-trimoxazole was associated with an increased risk of sudden death (adjusted odds ratio 1.38, 95% confidence interval 1.09 to 1.76). The risk was marginally higher at 14 days (adjusted odds ratio 1.54, 1.29 to 1.84). This corresponds to approximately three sudden deaths within 14 days per 1000 co-trimoxazole prescriptions. Ciprofloxacin (a known cause of QT interval prolongation) was also associated with an increased risk of sudden death (adjusted odds ratio 1.29, 1.03 to 1.62), but no such risk was observed with nitrofurantoin or norfloxacin.

Conclusions In older patients receiving angiotensin converting enzyme inhibitors or angiotensin receptor blockers, co-trimoxazole is associated with an increased risk of sudden death. Unrecognized severe hyperkalemia may underlie this finding. When appropriate, alternative antibiotics should be considered in such patients.

Introduction

Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are among the most commonly prescribed drugs in clinical practice. Each year, more than 50 million prescriptions are dispensed in the United Kingdom and more than 250 million prescriptions in the United States.[1 2] These drugs are principally used for the treatment of hypertension, coronary artery disease, congestive heart failure, proteinuria, and chronic kidney disease.[3] Both drug classes increase the risk of hyperkalemia, which occurs in up to 10% of patients and is particularly common in patients with other drug and disease related risk factors for hyperkalemia.[4-7]

Co-trimoxazole (a combination antibiotic containing trimethoprim and sulfamethoxazole) is commonly prescribed for the treatment of urinary tract infection and is listed on the World Health Organization's essential medicines list.[8] Each year, approximately five million prescriptions are dispensed in the United Kingdom and 20 million in the United States.[9 10] Trimethoprim has structural and pharmacologic similarities to

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the potassium sparing diuretic amiloride. At doses used in clinical practice (typically 80-160 mg twice daily), trimethoprim blocks the epithelial sodium channel (ENaC) in the distal nephron, impairing renal potassium elimination.[11 12] Approximately 80% of patients receiving co-trimoxazole develop increases in serum potassium concentrations of at least 0.36 mEq/L and 6% develop frank hyperkalemia (potassium >5.4 mEq/L).[13]

We have previously shown that the use of co-trimoxazole with angiotensin converting enzyme inhibitors or angiotensin receptor blockers results in an almost sevenfold increase in the risk of hyperkalemia related hospital admission relative to amoxicillin.[14] Case reports show that this drug interaction can cause life threatening hyperkalemia,[15 16] but whether it can increase the risk of sudden death in clinical practice is unknown. This is an important question, because sudden death due to hyperkalemia in the pre-hospital setting is likely to be misattributed to intrinsic heart disease, particularly in older patients with existing cardiovascular disease or diabetes.[17]

Co-trimoxazole induced hyperkalemia is common,[13 18] can occur quickly,[13 19] and can be life-threatening.[20] We examined whether treatment with co-trimoxazole was associated with a higher risk of sudden death than other antibiotics used for urinary tract infection in patients receiving angiotensin converting enzyme inhibitors or angiotensin receptor blockers.

Methods

Setting

We did a population based nested case-control study of Ontario residents aged 66 years or older receiving an angiotensin converting enzyme inhibitor or angiotensin receptor blocker between 1 April 1994 and 1 January 2012, the last date for which the vital statistics database was updated.

Data sources

We identified prescription drug claims by using the Ontario drug benefit database, which includes prescriptions dispensed to all Ontarians aged 65 years or older. We obtained hospital admission data from the Canadian Institute for Health Information's discharge abstract database, which contains detailed demographic and clinical information on admissions, discharges, and same day surgical procedures for all hospitals in Ontario. Additional demographic information came from the registered persons database, a registry of all Ontario residents with publically funded health insurance. We obtained physicians' claims data from the Ontario health insurance plan database and identified patients with diabetes by using the Ontario diabetes database.[21] We used the Ontario congestive heart failure database to identify people with heart failure.[22] We identified sudden death from the vital statistics database, which contains the cause of death listed on individual death certificates.[23] In Ontario, all death certificates are completed by the physician who last provided care to the patient, the patient's family physician, or a coroner. These databases are routinely used to conduct population based studies of drug safety, including the consequences of drug-drug interactions.[6-24] We linked them in an anonymous fashion by using encrypted health card numbers.

Identification of cases and controls

We identified patients treated with either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker between 1 April 1994 and 1 January 2012, excluding patients who received both drug classes simultaneously. For each patient, we defined a period of continuous drug use beginning with the first prescription after their 66th birthday and ending with death, discontinuation of treatment, or the end of the study period, whichever occurred first. We did not study patients during their first year of eligibility for prescription drug coverage (age 65) to avoid incomplete medication records. We deemed patients to have discontinued treatment if more than 100 days lapsed between successive prescriptions; in such cases, observation was extended for 100 days from the date of the last prescription.

Within the cohort of patients receiving an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, we defined case patients as those who died suddenly by using an approach validated previously (positive predictive value 87%).[25] This definition was validated using linked Medicaid databases and death certificates to identify international classification of disease (ICD) codes consistent with sudden death (that is, sudden death, conduction disorders, dysrhythmias).

The primary analysis examined sudden death within seven days of an outpatient prescription for one of co-trimoxazole, ciprofloxacin, norfloxacin, nitrofurantoin, or amoxicillin—antibiotics commonly used to treat urinary tract infections. With the exception of co-trimoxazole, none of these is an independent risk factor for severe hyperkalemia. We included ciprofloxacin because of its clinical popularity, although it is typically used for more complicated infections and can predispose to sudden death by prolonging the QT interval.[26-28] We excluded patients who received prescriptions for any other antibiotic in the 14 days preceding the index date, thereby restricting the analysis to patients with only one antibiotic prescription. The date of death served as the index date for all analyses.

For each case, we randomly selected up to four controls from the same cohort, matched on age (within 1 year), sex, and the presence or absence of kidney disease and diabetes, recognized risk factors for hyperkalemia and sudden death.[29 30] Each control could serve as a control only once, although they were eligible to become a case at a later date. Control patients were required to be alive at the index date and, like cases, received one of the study antibiotics in the seven days preceding the index date. To avoid the potential confounding effects of changes in antibiotic selection and prescribing practices over time, controls were assigned exactly the same index date as cases. We excluded cases that could not be matched to at least one control.

Statistical analysis

We used standardized differences to compare baseline characteristics of cases and controls. A standardized difference less than 0.1 indicates good balance between cases and controls for a given covariate.[31] We used conditional logistic regression to estimate the odds ratio and 95% confidence interval for the association between sudden death and recent antibiotic use. To prevent model over-fitting, we adjusted for an extensive array of covariates associated with the risk of sudden death by using a disease risk index in our adjusted analysis. A disease risk index is analogous to the propensity score used in cohort studies.[32] The disease risk index was derived from a non-parsimonious multivariable regression model that included sudden death as the dependent variable and an extensive list of medical comorbidities, drugs, recent procedures, recent emergency department visits, and several other variables that are related to the risk of sudden death (see web appendix).

The primary analysis examined the association between sudden death and receipt of a prescription for co-trimoxazole,

norfloxacin, nitrofurantoin, or ciprofloxacin in the preceding seven days. We used amoxicillin as the reference exposure because it is not an independent risk factor for hyperkalemia and is not associated with torsades de pointes. Because trimethoprim induced hyperkalemia may take longer to manifest clinically, we replicated our analyses using a 14 day period between antibiotic prescription and sudden death. In this analysis, we excluded patients who received prescriptions for any other antibiotic in the 21 days preceding the index date. To provide an approximation of the absolute risk of sudden death with co-trimoxazole, we did a supplementary analysis and calculated the number of sudden deaths within 14 days of receipt of either co-trimoxazole or amoxicillin. We used SAS version 9.3 for all analyses and a two sided type 1 error rate of 0.05 as the threshold for statistical significance.

Results

During the 17 year study period, we identified 1 601 542 patients treated with either an angiotensin converting enzyme inhibitor or angiotensin receptor blocker. Within this cohort, 39 879 died suddenly; of these deaths, 1110 occurred within seven days of a prescription for one of the study antibiotics. The vast majority of cases (1027; 93%) were matched to at least one control (3733 controls). Table 1⇓ shows the characteristics of cases and controls.

In the primary analysis, co-trimoxazole was associated with a significantly increased risk of sudden death within seven days relative to amoxicillin (unadjusted odds ratio 1.83, 95% confidence interval 1.50 to 2.24), and this result persisted after adjustment using the disease risk index (1.38, 1.09 to 1.76). Ciprofloxacin was also associated with a marginally lower but significant risk of sudden death (adjusted odds ratio 1.29, 1.03 to 1.62). We found no such risk with norfloxacin (adjusted odds ratio 0.74, 0.53 to 1.02) and a lower risk with nitrofurantoin (0.64, 0.46 to 0.88) (table 2⇓).

In a secondary analysis examining sudden death within 14 days of antibiotic prescription, we identified 1827 patients who died suddenly and were matched to at least one control (n=6771 controls). In this analysis, we again observed an increased risk of sudden death with co-trimoxazole relative to amoxicillin (adjusted odds ratio 1.54, 1.29 to 1.84). In contrast, we observed no increased risk of sudden death with the other antibiotics (table 3⇓).

In a supplementary analysis designed to test the robustness of our findings, we removed congestive heart failure (a known risk factor for sudden death) from the disease risk index and incorporated it as an independent term in the conditional logistic regression model. The results were not appreciably different from our primary analyses (see web appendix).

Discussion

In this population based study spanning 17 years, we found that co-trimoxazole was associated with sudden death in outpatients receiving angiotensin converting enzyme inhibitors or angiotensin receptor blockers. This corresponds to approximately three sudden deaths with co-trimoxazole compared with one sudden death with amoxicillin per 1000 prescriptions dispensed (see web appendix). We speculate that the increased risk of sudden death during treatment with co-trimoxazole reflects unrecognized arrhythmic death due to hyperkalemia, a well described complication of the use of trimethoprim in this setting.

Converging lines of evidence support the notion that terminal hyperkalemia may explain our findings. Clinical trials, case reports, and laboratory studies show that co-trimoxazole induced hyperkalemia can occur quickly and can cause life threatening arrhythmias, especially among patients receiving angiotensin converting enzyme inhibitors or angiotensin receptor blockers.[13-34] Our previous research on this drug interaction showed a nearly sevenfold increased risk of hospital admission with hyperkalemia following co-trimoxazole treatment but no such risk with the same alternative antibiotics studied here.[14] In the analysis presented here, we found no increased risk of sudden death with nitrofurantoin or norfloxacin.

Ciprofloxacin was also associated with an increased risk of sudden death, although this dissipated in the 14 day analysis. Ciprofloxacin can prolong the QT interval and cause torsades de pointes in susceptible patients.[27-37] Ciprofloxacin induced QT prolongation occurs early in the course of treatment and generally resolves when treatment is stopped;[25 37] this may explain why the effect was attenuated in the 14 day analysis. Importantly, ciprofloxacin also tends to be used in patients with more severe or complicated urinary tract infections.[38] Whether QT prolongation, severity of illness, or different indications explain the risk associated with ciprofloxacin is unclear.

Nitrofurantoin was associated with a lower risk of sudden death for the seven day analysis, but not the 14 day analysis. The decreased risk for the seven day analysis may be spurious, given the relatively small sample size, and may reflect selection of patients, as nitrofurantoin is generally reserved for uncomplicated urinary tract infections.

Limitations

Some limitations of our study merit emphasis. Our findings derive from patients aged 66 years and older, and the generalizability to younger patients is unknown. Although we used a validated algorithm to define sudden death,[25] some degree of outcome misclassification is likely. However, this applies equally to all the antibiotics we studied. We used administrative data and did not have access to serum potassium or creatinine concentrations, adherence to treatment, non-prescription drug use, and other risk factors for sudden death. Again, these limitations are independent of antibiotic exposure. Whereas nitrofurantoin and norfloxacin are limited to the treatment of urinary tract infection, amoxicillin, co-trimoxazole, and ciprofloxacin are sometimes used for infections at other sites. Although we had no information on indications for antibiotic use, we used a disease risk index to adjust for potential predictors of sudden death. Finally, we were unable to reliably determine the dose of trimethoprim, precluding a dose-response analysis. Doing such an analysis may have further strengthened the argument that hyperkalemia underlies our main observations.

Conclusion and implications

We found that use of co-trimoxazole was associated with an increased risk of sudden death in older patients taking angiotensin converting enzyme inhibitors or angiotensin receptor blockers. We speculate that this association reflects sudden death from co-trimoxazole induced hyperkalemia in a vulnerable group of patients. The importance of our findings is underscored by the fact that co-trimoxazole is prescribed to millions of patients taking angiotensin converting enzyme inhibitors or angiotensin receptor blockers. Sudden death in these patients is likely to be misattributed to underlying cardiovascular disease, rather than hyperkalemia.

We suggest that, when clinically appropriate, clinicians either choose alternate antibiotics or limit the dose and duration of co-trimoxazole treatment. When co-trimoxazole is prescribed, close monitoring of serum potassium is advisable in susceptible patients.

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Ethical approval: This study was approved by the research ethics board of Sunnybrook Health Sciences Centre, Toronto, Ontario.

Declaration of transparency: The lead author (study guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing: No additional data available.

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What is already known on this topic

The prescribing of co-trimoxazole with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) results in a sevenfold increase in the risk of hospital admission with hyperkalemia relative to amoxicillin

Case reports have shown that this drug interaction can cause life threatening hyperkalemia

What this study adds

In older patients receiving ACE inhibitors or ARBs, co-trimoxazole was associated with an increased risk of sudden death; this may reflect sudden death from unrecognized severe hyperkalemia

When patients receiving ACE inhibitors or ARBs require an antibiotic, clinicians should either select antibiotics that do not contain trimethoprim or limit the dose and duration of trimethoprim based therapies, while closely monitoring the serum potassium concentration

Tables

Table 1| Characteristics of cases and controls. Values are numbers (percentages) unless stated otherwise

Characteristic	Cases (n=1027)	Controls (n=3733)	Standardized difference
Median (IQR) age (years)	82 (75-87)	82 (75-87)	0.03
Age group (years):			
65 to 74	244 (23.8)	870 (23.3)	0.01
75 to 84	392 (38.2)	1483 (39.7)	0.03
≥85	391 (38.1)	1380 (37.0)	0.02
Male sex	388 (37.8)	1352 (36.2)	0.03
Charlson score:			
0	233 (22.7)	1927 (51.6)	0.60
1	176 (17.1)	680 (18.2)	0.03
≥2	618 (60.2)	1126 (30.2)	0.64
Income fifth:			
1 (lowest)	275 (26.8)	841 (22.5)	0.10
2	201 (19.6)	821 (22.0)	0.06
3	200 (19.5)	720 (19.3)	0
4	152 (14.8)	711 (19.0)	0.11
5 (highest)	189 (18.4)	618 (16.6)	0.05
Missing	10 (1.0)	22 (0.6)	
Median (IQR) years using ACEI/ARB	1 (0-3)	3 (1-5)	0.56
Median (IQR) No of distinct drugs prescribed in previous year	15 (11-20)	13 (9-17)	0.35
Diabetes	315 (30.7)	1091 (29.2)	0.03
Renal disease	84 (8.2)	134 (3.6)	0.22
Heart failure	454 (44.2)	886 (23.7)	0.46
Drug use in previous 90 days:			
Non-potassium sparing diuretics	134 (13.0)	526 (14.1)	0.03
Potassium sparing diuretics	113 (11.0)	268 (7.2)	0.14
Loop diuretics	732 (71.3)	1505 (40.3)	0.64
β adrenergic antagonists	254 (24.7)	783 (21.0)	0.09
Potassium supplements	28 (2.7)	69 (1.8)	0.06
NSAIDs	128 (12.5)	619 (16.6)	0.11

ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; IQR=interquartile range; NSAID=non-steroidal anti-inflammatory drug.

Table 2| **Antibiotic use and risk of sudden death within seven days**

Antibiotic use	No (%) cases	No (%) controls	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)*
Amoxicillin (reference)	226 (22.0)	1098 (29.4)	1.0 (reference)	1.0 (reference)
Co-trimoxazole	288 (28.0)	734 (19.7)	1.83 (1.50 to 2.24)	1.38 (1.09 to 1.76)
Ciprofloxacin	340 (33.1)	964 (25.8)	1.66 (1.37 to 2.00)	1.29 (1.03 to 1.62)
Norfloxacin	79 (7.7)	455 (12.2)	0.81 (0.61 to 1.08)	0.74 (0.53 to 1.02)
Nitrofurantoin	94 (9.2)	482 (12.9)	0.87 (0.66 to 1.15)	0.64 (0.46 to 0.88)

*Analysis adjusted for disease risk index.

Table 3| **Antibiotic use and risk of sudden death within 14 days**

Antibiotic use	No (%) cases	No (%) controls	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)*
Amoxicillin (reference)	418 (22.9)	2021 (29.8)	1.0 (reference)	1.0 (reference)
Co-trimoxazole	474 (25.9)	1262 (18.6)	1.80 (1.54 to 2.09)	1.54 (1.29 to 1.84)
Ciprofloxacin	603 (33.0)	1888 (27.9)	1.50 (1.30 to 1.72)	1.18 (1.00 to 1.39)
Norfloxacin	158 (8.6)	832 (12.3)	0.89 (0.73 to 1.09)	0.83 (0.65 to 1.05)
Nitrofurantoin	174 (9.5)	768 (11.3)	1.08 (0.88 to 1.32)	1.03 (0.81 to 1.30)

*Analysis adjusted for disease risk index.