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A population-based assessment of the potential interaction between serotonin-specific reuptake inhibitors and digoxin

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Aim
In vitro evidence suggests that some serotonin-specific reuptake inhibitors (SSRIs) inhibit P-glycoprotein, a multidrug efflux pump responsible for the elimination of several drugs including digoxin. We sought to determine if some SSRIs cause digoxin toxicity in the clinical setting.

Methods
Population-based nested case–control study set in Ontario, Canada from 1994 to 2001. We studied all patients 66 years or older treated with digoxin. Prescription and hospital admission records were analysed to determine the relationship between the initiation of SSRI therapy and hospital admission for digoxin toxicity in the subsequent 30 days.

Results
Among 245 305 older patients treated with digoxin, we identified 3144 cases of digoxin toxicity. After adjusting for potential confounders, we observed an increased risk of digoxin toxicity following initiation of paroxetine [odds ratio (OR) 2.8; 95% confidence interval (CI) 1.6, 4.7], fluoxetine (OR 2.9; 95% CI 1.5, 5.4), sertraline (OR 3.0; 95% CI 1.9, 4.7), and fluvoxamine (OR 3.0; 95% CI 1.5, 5.7). However, an elevated risk was also seen with tricyclic antidepressants (OR 1.5; 95% CI 1.0, 2.4) and benzodiazepines (OR 2.1; 95% CI 1.7, 2.5), drugs classes having no known pharmacokinetic interaction with digoxin. There was no statistical difference in the risk of digoxin toxicity among any of the agents tested.

Conclusions
We found no major discrepancy in the risk of digoxin toxicity after initiation of various SSRI antidepressants, suggesting that the inhibition of P-glycoprotein by sertraline and paroxetine observed *in vitro* is unlikely to be of major clinical significance.

Introduction

Over the past decade, serotonin-specific reuptake inhibitors (SSRIs) have become increasingly popular for the treatment of depression and other psychiatric disorders [1]. Although they are effective and generally well tolerated, they can occasionally provoke serious drug–drug interactions by inhibiting the hepatic metabolism of other drugs. While the differential effects of various SSRIs on the hepatic cytochrome P450 (CYP450) enzyme system are well characterized [2, 3], it is unclear whether these drugs might have additional influences on drug disposition.

The multidrug efflux transporter P-glycoprotein (P-gp) regulates the absorption and elimination of many drugs. This pump acts as a natural defence mechanism against several substrates by limiting their absorption from the gut and promoting their elimination in the bile and urine [4]. In an analogous fashion to CYP450 enzymes, the activity of P-gp can be inhibited or induced by treatment with other drugs, altering the level of substrate drugs in circulation. For example, dexamethasone induces P-gp, whereas erythromycin, quinidine, and verapamil inhibit its activity.

Evidence suggests that some newer antidepressants may inhibit the activity of P-gp [5]. For example, a recent *in vitro* study using L-MDR1 cells found IC_{50} values of 31.8 μM for sertraline and 29.8 μM for paroxetine, comparable to that of quinidine (33.8 μM), a prototypical P-gp inhibitor. In contrast, fluoxetine (IC_{50} 115.5 μM) and fluvoxamine (IC_{50} not definable) exhibited no significant P-gp inhibition. It remains unclear, however, whether the differential inhibition of P-gp observed *in vitro* is a clinically relevant feature of SSRIs in clinical practice. While some case reports describe digoxin toxicity during antidepressant therapy [6, 7], volunteer studies suggest no such interaction [8–10].

Many substrates for P-gp (such as cyclosporin, digoxin, and various chemotherapeutic agents) have a narrow therapeutic range and can cause serious toxicity when P-gp inhibitors are administered concurrently. Differential inhibition of P-gp by SSRI antidepressants would be particularly important given that more than 1 in 10 older patients are treated with these drugs [1]. Using digoxin as a prototypical P-gp substrate, we examined the association between various SSRIs and digoxin toxicity in a population of more than 1.3 million patients by employing a novel approach for the assessment of drug–drug interactions using administrative data [11].

Methods

Setting and design

This was a population-based nested case–control study linking multiple healthcare databases over 8 years (1 January 1994 to 31 December 2001) in Ontario, Canada. Ontario is Canada's most populous province, with a population of about 13 million of whom approximately 1.5 million are ≥65 years old [12]. These patients have universal access to hospital care, physicians' services, and prescription drug coverage from a minimally restrictive formulary. Databases containing the healthcare records of individual patients can be linked and analysed in an anonymous fashion using encrypted 10-digit healthcard numbers. This research project was approved by the ethics review board of Sunnybrook and Women's College Health Sciences Centre.

Data sources

We examined the computerized prescription records of the Ontario Drug Benefit Programme, which records prescription drugs dispensed to all Ontario residents ≥65 years of age. The overall error rate in the database is <1% [13]. Hospitalization records were obtained from the Canadian Institute for Heath Information Discharge Abstract Database, which contains a detailed record of all hospital admissions. The Ontario Health Insurance Plan provides physician claims information for inpatient and outpatient services, and the Ontario Registered Persons Database contains basic demographic information for each Ontario resident. These databases have been analysed previously to study other population-based health outcomes [14–18].

Selection of probe drug

We examined the influence of individual SSRIs on the risk of digoxin toxicity. We selected digoxin as a probe drug because it is a commonly used medication with a narrow therapeutic range, and because P-gp inhibition consistently elevates digoxin levels [19]. Importantly, digoxin is not subject to phase I metabolism by cytochrome P450 enzymes, many of which exhibit varying degrees of inhibition by different SSRI antidepressants. Moreover, digoxin toxicity is a characteristic clinical syndrome that is readily identifiable using administrative data. For example, we recently documented a 12-fold increase in the risk of hospital admission for digoxin toxicity following treatment with clarithromycin, a macrolide antibiotic known to inhibit P-gp [11].

Observation period

For each patient treated with digoxin, we studied a period of continuous use beginning with the first prescription following their 66th birthday, and ending with hospital admission for digoxin toxicity (ICD-9972.1), the end of the study period, death, or discontinuation of the study medication (whichever occurred first.) Subjects were considered to discontinue 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.

Case and control patients

Within the cohort of continuous users of digoxin, we defined case patients as those admitted to hospital with

digoxin toxicity (ICD-9 972.1). We excluded cases of intentional overdose by removing cases with an external cause of injury code (E-code) E950, which denotes intentional self-harm [20]. The date of admission served as the index date for all analyses, and only the first event was considered for patients admitted more than once with digoxin toxicity. For each case, we selected up to 50 control patients, matching on age, gender, and continuous use of digoxin on the index date. When numerous potential controls existed for a case, 50 were randomly chosen for analysis. When fewer than 50 potential controls were available, we analysed only those available controls and maintained the matching process.

Exposure to SSRIs

For each case and control patient we identified new prescriptions for fluoxetine, fluvoxamine, sertraline, and paroxetine in the 30 days preceding the index date. We focused on this exposure window because digoxin toxicity is likely to manifest shortly following the addition of a P-gp inhibitor [19]. Case and control patients who received additional SSRI prescriptions in the 6 months prior to the index date were excluded from the analysis. We did not examine prescriptions for other newer antidepressants (including citalopram, venlafaxine, trazodone, and bupropion) because they were not in widespread use in Ontario during much of our study period.

To place our findings in context, we also examined prescriptions for tricyclic antidepressants (TCAs) and benzodiazepines. Both of these drug classes are prescribed to older patients for a variety of indications, but neither is known to inhibit P-glycoprotein or cause digoxin toxicity. As a final test of specificity, we examined prescriptions for topical corticosteroid creams because they have no plausible association with digoxin toxicity.

Statistical analysis

Conditional logistic regression was used to estimate the odds ratio and associated 95% confidence intervals for the association between SSRI use and hospital admission for digoxin toxicity. We performed multivariate adjustment for diagnoses and receipt of other medications that might influence the risk of digoxin toxicity, in a fashion described previously [11]. We adjusted for renal insufficiency by examining inpatient and outpatient records (physician claims, inpatient diagnostic codes, and haemodialysis records) in the 2 years prior to and including the index date for any evidence of renal impairment. We also adjusted for receipt of other common P-gp inhibitors (amiodarone, clarithromycin, erythromycin, ketoconazole, itraconzaole, quinidine, and verapamil), P-gp inducers (dexamethasone and rifampin), and other antidepressants in the 90 days preceding the index date [4]. Finally, patients with a previous history of digoxin toxicity may have more subtle reasons to experience a recurrence, so we also adjusted for any history of hospitalization for digoxin toxicity in the 2 years prior to cohort entry. All two-way comparisons between adjusted odds ratios were conducted using standard methods [21], and all analyses were performed using SAS version 8.2 (The SAS Institute, Cary, NC, USA).

Results

Primary analyses

We identified 245 305 elderly patients treated with digoxin continuously for a total of 579 103 patient-years of therapy. Of these, 33 147 (14%) also received at least one prescription for an antidepressant. The mean (SD) age of patients treated with digoxin was 77.8 (± 7.8) years and about half (54%) were women.

The characteristics of cases and controls are shown in Table 1. During the 8-year period, 3144 patients were admitted to hospital with digoxin toxicity, equivalent to about one case for every 184 person-years of treatment, or more than one patient in Ontario each day. Cases were, on average, about 3 years older than other patients receiving digoxin and were significantly more likely (63%) than the rest of the cohort to be women. The median length of hospital stay for digoxin toxicity was about 7 days, and 344 patients (11%) died prior to discharge. Compared with controls, patients admitted with digoxin toxicity received more prescription medications in the preceding year (median 15 *vs.* 11, respectively) and were more likely to have a documented history of renal disease (38% *vs.* 17%, respectively).

Patients admitted with digoxin toxicity were significantly more likely than controls to have received a new prescription for any of sertraline, fluoxetine, fluvoxamine, or paroxetine in the 30 days prior to admission (Table 2). Multivariate adjustment for use of other P-gp inhibitors, a history of renal disease or previous admission for digoxin toxicity yielded similar results. TCAs and benzodiazepines were both associated with a significant but somewhat lower risk of digoxin toxicity, although analysis of all possible two-way comparisons among the various SSRIs, TCAs, and benzodiazepines revealed no statistically significant differences for any drug or drug class (all P-values >0.16). As expected, we found no significant association between digoxin toxic-

Table 1
Characteristics of cases and controls

Characteristic	Cases (n = 3144)	Controls (n = 156 650)
Age (years), mean (SD)	80.9 (7.4)	80.8 (7.3)
Gender		
Men, *n* (%)	1170 (37%)	58173 (37%)
Women, *n* (%)	1974 (63%)	98477 (63%)
Duration of digoxin therapy (years), mean (SD)	2.0 (2.0)	2.5 (2.0)
Number of drugs dispensed in preceding year, median (IQR)	15 (11–21)	11 (7–15)
Documented renal disease, *n* (%)	1181 (38%)	26216 (17%)

Table 2
Risk of digoxin toxicity within 30 days of commencing treatment with various antidepressants

	Cases (n = 3144)	Controls (n = 156 650)	Univariate odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
SSRIs				
Sertraline	22 (0.70%)	260 (0.17%)	4.3 (2.8, 6.6)	3.0 (1.9, 4.7)
Fluoxetine	11 (0.35%)	129 (0.08%)	4.3 (2.3, 7.9)	2.9 (1.5, 5.4)
Fluvoxamine	11 (0.35%)	113 (0.07%)	4.9 (2.6, 9.1)	3.0 (1.5, 5.7)
Paroxetine	16 (0.51%)	191 (0.12%)	4.2 (2.5, 7.0)	2.8 (1.6, 4.7)
Comparators				
Cyclic antidepressants	24 (0.76%)	535 (0.34%)	2.3 (1.5, 3.4)	1.5 (1.0, 2.3)
Benzodiazepines	109 (3.47%)	2155 (1.38%)	2.6 (2.1, 3.1)	2.1 (1.7, 2.5)
Topical steroids	78 (2.48%)	3307 (2.11%)	1.2 (0.9, 1.5)	1.0 (0.8, 1.2)

**Adjusted for use of other interacting drugs, documented renal disease, and previous admissions for digoxin toxicity.*

ity and exposure to topical corticosteroids in the preceding month.

Discussion

Among nearly a quarter of a million older patients receiving digoxin, we identified a slightly increased short-term risk of admission for digoxin toxicity immediately following the initiation of SSRI therapy. However, the association was far weaker than the 12-fold higher risk seen with the use of clarithromycin, a known inhibitor of P-gp [11, 22]. Moreover, the risk was not statistically different from that found with TCAs or benzodiazepines, drugs not known to inhibit P-gp or provoke digoxin toxicity.

Although recent *in vitro* evidence suggests that sertraline and paroxetine may be more likely than other SSRIs to inhibit P-gp, neither was associated with a disproportionately higher risk of digoxin toxicity than fluoxetine or fluvoxamine. The lack of a difference suggests that P-gp inhibition by SSRIs is unlikely to be of major clinical relevance, and the finding is particularly important because about one in seven elderly patients treated with digoxin also received at least one prescription for an antidepressant during our study period.

We speculate that factors other than P-gp inhibition underlie the associations between psychotropic medication use and digoxin toxicity observed in our study. Physicians are more likely to prescribe SSRIs than TCAs in older patients with comorbid illness, and this may introduce detection bias if SSRI-treated patients undergo more frequent medical assessments or therapeutic drug monitoring. Moreover, TCAs are not used exclusively for depression, and an element of con-

founding by indication may contribute to the statistically significant association between SSRIs and digoxin toxicity [23, 24]. Specifically, although we excluded episodes of digoxin toxicity where intentional overdose was evident, E-codes are imperfect for this purpose [20]. As a result, some SSRI-treated patients with intentional digoxin overdose may have been retained as cases in our analysis. However, such misclassification would be common to all SSRIs and would not explain the nearly identical risk of digoxin toxicity among the various agents.

Several limitations of our study merit emphasis. We used administrative data and have no direct measure of drug levels, renal function, or adherence to medications. The accuracy of hospital discharge coding for digoxin toxicity is unknown, and some cases may have been intentional. Finally, we were unable to test for an association between other new antidepressants (such as citalopram and venlafaxine) and digoxin toxicity. Conversely, the study has several strengths, including a large population-based sample and the efficiency of case–control methodology, which may be the most sensitive approach for the detection of drug–drug interactions using administrative data. Importantly, unlike most studies of drug–drug interactions, ours provides a clinical perspective using ambulatory patients rather than healthy volunteers.

In summary, despite recent *in vitro* data suggesting that sertraline and paroxetine may inhibit P-gp, our findings imply that this is unlikely to be of major clinical significance. Further prospective studies are warranted to confirm these observations. In the interim, although drug–drug interactions remain an important consideration when selecting an antidepressant, treatment decisions should not be unduly influenced by concerns about P-gp inhibition.

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