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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Ciprofloxacin-induced theophylline toxicity: a population-based study

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Abstract
Purpose Ciprofloxacin can inhibit the cytochrome P450-mediated metabolism of theophylline, but the clinical relevance of this drug interaction is uncertain. We studied the risk of theophylline toxicity associated with the co-prescription of ciprofloxacin and theophylline.

Methods This was a population-based, nested case–control study of a cohort of Ontario residents aged 66 years of age or older treated with theophylline between April 1, 1992 and March 31, 2009. Within this group, case patients were those hospitalized with theophylline toxicity. For each case, 50 age- and sex-matched control patients were identified from the same cohort. The odds ratio (OR) for the association between hospitalization for theophylline toxicity and receipt of ciprofloxacin in the 14 days preceding hospitalization was determined.
Results Among the 77,251 elderly patients receiving therapy with theophylline, 180 eligible case patients hospitalized for theophylline toxicity and 9000 matched controls were identified. Following multivariable adjustment, a nearly twofold increase in the risk of theophylline toxicity following the receipt of ciprofloxacin was observed [adjusted OR 1.86, 95% confidence interval (CI) 1.18–2.93]. In contrast, there was no increased risk of theophylline toxicity within a group of patients receiving neutral comparator antibiotics (levofloxacin, trimethoprim-sulfamethoxazole or cefuroxime) (adjusted OR 0.78; 95% CI 0.38–1.62).
Conclusion Treatment with ciprofloxacin is associated with a significant increase in the risk of theophylline toxicity. When clinically appropriate, alternate antibiotics should be considered for elderly patients receiving theophylline.

Keywords Ciprofloxacin · Ciprofloxacin/adverse effects · Drug interactions · Theophylline/poisoning

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Introduction

Despite a decline in its popularity, theophylline remains a commonly used drug for the management of chronic respiratory disease [1]. Results from randomized controlled

trials affirm the efficacy of theophylline in patients with stable chronic obstructive pulmonary disease (COPD), and those from recent studies suggest that low doses of the drug elicit anti-inflammatory and immunomodulatory effects that are distinct from, and synergistic with, those of corticosteroids [2–7]. Consequently, there has been renewed interest in the use of theophylline as an adjunct to first-line therapies in patients with airway disease [7–9].

However, in clinical practice, the use of theophylline is limited by a narrow therapeutic range and concentration-related toxicity that ranges in severity from nausea, tremor and headache, to more serious sequelae, such as seizures and life-threatening cardiac dysrhythmias [1]. The concentration-dependent nature of theophylline elimination poses an additional challenge to the safe use of this drug because serum levels can increase dramatically following relatively small increases in dose or changes in metabolic clearance, placing patients at risk of inadvertent theophylline toxicity [10, 11]. Risk factors for theophylline toxicity have been well described and include the use of alcohol, hypothyroidism, chronic liver disease and congestive heart failure [12].

Drug interactions are an important and avoidable cause of theophylline toxicity [13–15]. Theophylline biotransformation is catalyzed principally by the 1A2 isoenzyme of the cytochrome P450 system (CYP1A2) [16, 17]. Consequently, the concomitant administration of drugs that can inhibit this enzyme may predispose patients to theophylline toxicity. Ciprofloxacin is a potent inhibitor of the CYP1A2 isoenzyme and is commonly used for the management of acute exacerbations of chronic bronchitis and *Pseudomonas aeruginosa* infections in patients with bronchiectasis [18–21]. In a number of pharmacokinetic studies, theophylline clearance was reduced by 19–32% following treatment with ciprofloxacin [22–28]. Given the saturable nature of theophylline metabolism, decreases in theophylline clearance of this magnitude could be clinically significant. At the present time, however, the clinical consequences of this interaction are described only in case reports [29–33].

Given that ciprofloxacin is a commonly used antibiotic in patients with COPD, the likelihood of co-prescription with theophylline is high. However, the excess risk of theophylline toxicity following the use of ciprofloxacin has not been studied at the population level. The aim of the study reported here was to characterize the clinical significance of this drug interaction in clinical practice.

Methods

This was a population-based, nested case–control study of Ontario residents 66 years of age or older who were treated with theophylline between April 1, 1992 and March 31, 2009. Prescription medications were identified using the records of the Ontario Drug Benefit (ODB) Program, which identifies prescriptions dispensed to all Ontario residents aged 65 years or older. We did not examine the first year of eligibility for prescription drug benefits (age 65 years) to avoid incomplete medication records, and patients younger than 65 years were excluded because prescription records for this group of patients are not available in the ODB database. Hospitalization data and demographic information were obtained from the Canadian Institute for Health Information Discharge Abstract Database (DAD) and Registered Persons Database, respectively. The DAD contains demographic and clinical information regarding hospital admissions and discharges from participating hospitals in Canada. Abstraction of patient charts in the DAD is undertaken by trained health information professionals using standard diagnosis and procedure codes. Finally, the Ontario Health Insurance Plan database was used to identify claims for physician services. These three databases were linked in an anonymous fashion using encrypted health card numbers and have been used previously to study population-based health outcomes, including the consequences of drug–drug interactions [34–37].

For each patient, we identified a period of continuous theophylline use beginning with the first prescription for theophylline following the patient's 66th birthday. The observation period ended with the first hospitalization for theophylline toxicity, death or cessation of theophylline treatment, defined as a lapse of more than 100 days between prescriptions. In these instances, the observation period was extended 100 days beyond the date of the last prescription in order to identify outcomes that may have precipitated the cessation of treatment.

Within the cohort of continuous users of theophylline, cases were defined as those hospitalized with a diagnosis of theophylline toxicity (International Classifications of Diseases: 9th edition, codes 974.1, 975.7, 975.8; 10th edition, codes T48.6 and T48.7). The analysis was restricted to patients with theophylline toxicity as an admission diagnosis, as opposed to those in whom toxicity emerged during the course of hospitalization. The date of hospitalization served as the index date for all analyses, and only the first hospitalization for theophylline toxicity was considered for patients with more than one such admission during the study period.

From within the cohort of patients receiving theophylline, up to 50 controls for each case patient were selected using incidence density sampling [38]. Controls and cases were matched on age at the index date (±3 years) and sex. When fewer than 50 available controls could be matched to

each case, we analyzed only those controls and maintained the matching process.

The ODB database was used to identify prescriptions for ciprofloxacin in the 14 days prior to the index date for each case and control patient. A 14-day exposure window was selected to provide sufficient time for complete inhibition of CYP1A2 following treatment with ciprofloxacin, attainment of maximal theophylline levels and presentation to hospital following the onset of symptoms of theophylline toxicity. To test the specificity of the findings, we also examined exposure to a combined group of neutral comparator antibiotics (levofloxacin, trimethoprim/sulfamethoxazole, and cefuroxime) which have similar clinical indications as ciprofloxacin, but which would not be expected to inhibit theophylline metabolism or provoke theophylline toxicity. Case and control patients who received prescriptions for multiple exposure antibiotics and those who received a non-study antibiotic in the 30 days preceding the index date were excluded from the analysis.

Statistical analysis

Descriptive statistics were calculated for baseline demographic and clinical characteristics of cases and controls, and standardized differences were computed to test for differences between the two groups. Standardized differences can be used to directly quantify the balance in means or proportions of covariates between matched cases and controls and are expressed here as percentages of pooled standard deviations (SD). They are therefore not confounded by sample size and illustrate where clinically meaningful differences between cases and controls may exist. A standardized difference of <0.1 indicates good balance between cases and controls for a given covariate [39].

Conditional logistic regression was used to estimate the odds ratio (OR) and 95% confidence intervals (CIs) for the association between hospitalization for theophylline toxicity and antibiotic use in the preceding 14 days. Patients not treated with an antibiotic served as the reference group. Multivariable conditional logistic regression analysis was performed to adjust for concomitant medical conditions and other medications that could influence the risk of theophylline toxicity (Appendix 1). Other factors adjusted for include income quintile, residence in a long-term care facility, number of prescription drugs dispensed in the preceding year [40] and history of hospitalization for theophylline toxicity in the 1-year period prior to cohort entry. All analyses were performed using SAS ver. 9.2 (SAS Institute, Cary, NC). The study was approved by the Research Ethics Board of Sunnybrook Health Sciences Center.

Results

Over the course of the 18-year study period, we identified 77,251 individuals aged 66 years or older treated with theophylline. Of these, 14,746 (19.1%) received at least one prescription for ciprofloxacin while receiving theophylline. A total of 239 patients in the cohort were hospitalized for theophylline toxicity, and 180 met the inclusion criteria for the study. All cases were matched to 50 controls and included in the analysis. As expected, case patients exhibited a greater degree of co-morbidity, received more prescription drugs in the year preceding chohort entry and were more likely to have been previously hospitalized for theophylline toxicity (Table 1).

Following multivariable adjustment, patients hospitalized for theophylline toxicity were found to be almost twice as likely to have received ciprofloxacin [adjusted odds ratio (aOR) 1.86; 95% CI 1.18–2.93] in the preceding 14 days as compared with no antibiotic exposure (Table 2). In contrast, no such association was found with the neutral comparator antibiotics levofloxacin, trimethoprim/sulfamethoxazole and cefuroxime (aOR 0.78; 95% CI 0.38–1.62).

Discussion

In this population-based study spanning 18 years, we found a significant association between ciprofloxacin use and hospitalization for theophylline toxicity. In contrast, no such risk was seen with a neutral comparator group of antibiotics comprised of levofloxacin, trimethoprim/sulfamethoxazole and cefuroxime, highlighting the specificity of our findings with ciprofloxacin. Overall, our findings support the notion of a clinically meaningful drug interaction between ciprofloxacin and theophylline at the population level and augment the findings of previous pharmacokinetic investigations in this area by providing an estimate of the relative risk of theophylline toxicity associated with this drug combination in clinical practice.

Our findings have important clinical implications. In our cohort, approximately 20% of patients received at least one prescription for ciprofloxacin during the study period, thereby being placed at excess risk of theophylline toxicity. Although inadvertent theophylline toxicity is rarely fatal, it is a preventable form of drug-related harm that may be associated with considerable morbidity and cost to the health care system. Consequently, strategies aimed at minimizing the risk of theophylline toxicity are necessary co-requisites of treatment, particularly in vulnerable groups such as the elderly. When possible, minimizing the use of drugs that inhibit theophylline metabolism is recommended. When patients receiving theophylline require treatment

Table 1 Characteristics of cases and controls

Variable[a]	Cases (n=180)	Controls (n = 9000)	Standardized difference[b]
Age, years [median IQR)]	77 (72–82)	76 (72–81)	0.06
66–75	72 (40.0%)	4,057 (45.1%)	0.10
76–85	86 (47.8%)	4,029 (44.8%)	0.06
≥86	22 (12.2%)	914 (10.2%)	0.07
Male [n (%)]	84 (46.7%)	4,200 (46.7%)	0.00
Number of years of theophylline treatment [median (IQR)]	1 (0–3)	2 (1-4)	0.25
Residence in a long-term care facility	12 (6.7%)	459 (5.1%)	0.07
Number of prescription drugs in previous year [median (IQR)]	15 (11–19)	8 (4–13)	0.95
Previous hospitalization for theophylline toxicity (1 year)	≤ 5 (0.6%)	7 (0.1%)	0.16
Chronic liver disease in preceding year	≤ 5 (1.1%)	37 (0.4%)	0.11
Chronic alcoholism in preceding year	10 (5.6%)	139 (1.5%)	0.32
Congestive heart failure	31 (17.2%)	499 (5.5%)	0.50
Hypothyroidism	≤ 5 (2.2%)	66 (0.7%)	0.17
Pneumonia	26 (14.4%)	476 (5.3%)	0.40
Medication use in preceding 90 days			
CYP1A2 inhibitors	23 (12.8%)	471 (5.2%)	0.34
CYP3A4 inhibitors	40 (22.2%)	1,209 (13.4%)	0.26
CYP1A2/3A4 inducers	6 (3.3%)	164 (1.8%)	0.11
Income quintile			
1 (lowest)	54 (30.0%)	2,407(26.7%)	0.07
2	38 (21.1%)	1,894 (21.0%)	0.00
3	41 (22.8%)	1,585 (17.6%)	0.14
4	26 (14.4%)	1,437 (16.0%)	0.04
5	15 (8.3%)	1,343 (14.9%)	0.19
Missing	6 (3.3%)	334 (3.7%)	0.02

IQR, Interquartile range; CYP, cytochrome P450

[a] Unless indicated otherwise, data are given as the number (n) of patients, with the percentage of respective cohort (case or control) given in parenthesis

[b] Difference between cases and controls divided by standard deviation (SD)

with antibiotics, avoidance of ciprofloxacin may be advisable, when clinically appropriate.

Some limitations of our work merit emphasis. We used administrative data and had no data on theophylline levels, indication for antibiotic therapy, smoking status or medication adherence. In addition, the accuracy of hospital discharge coding for theophylline toxicity is unknown. Importantly, however, these limitations apply equally to

Table 2 Association between antibiotic use and hospitalization for theophylline toxicity

Antibiotic exposure in past 14 days	Patients		Crude OR[a](95% CI)	Adjusted OR[a, b] (95% CI)
	Cases (n=180)	Controls (n=9000)		
Ciprofloxacin	25 (13.9)	567 (6.3)	2.39 (1.55–3.69)	1.86 (1.18–2.93)
Neutral comparator antibiotics[c]	8 (4.4)	484 (5.4)	0.90 (0.44–1.84)	0.78 (0.38–1.62)

OR, Odds ratio; CI, confidence interval

Data are given as the number of cases (controls), with the percentage of respective group in parenthesis

[a] Referent group: no antibiotic exposure in past 14 days

[b] Adjusted for age category, hospitalization for theophylline toxicity in previous year, chronic disease (alcoholism, hepatic, congestive heart failure, hypothyroidism), pneumonia, income quintile, living in long-term care facility, number of prescription drugs in previous year, number of years of theophylline treatment and interacting medications in previous 90 days (Appendix 1)

[c] Neutral comparator antibiotics: levofloxacin, trimethoprim-sulfamethoxazole and cefuroxime

both ciprofloxacin and the comparator antibiotics. In addition, our analysis focused on outcomes related to hospital admission, and we therefore did not identify cases of theophylline toxicity managed in emergency departments or in the ambulatory setting. As such, our study may underestimate the clinical consequences of this drug interaction. We also restricted our outcome to hospitalizations for theophylline toxicity and did not consider other potential surrogates of theophylline toxicity, such as admissions for seizures or dysrhythmias. It is therefore possible that some cases of theophylline toxicity were missed by our analysis. Because some clinicians may appreciate the risk of theophylline toxicity associated with the use of ciprofloxacin, differential outcome ascertainment is a possible source of bias, although this is unlikely affecting our findings, given that theophylline levels are routinely measured at the time of hospital admission. Furthermore, our findings may not be applicable to younger patients with fewer risk factors for theophylline toxicity. Finally, our cases and controls differed at baseline with respect to variables which may act as important confounders in the relationship between ciprofloxacin use and theophylline toxicity. However, this applies to both ciprofloxacin and the neutral comparators, rendering it an unlikely explanation for our findings.

In conclusion, we found that the prescription of ciprofloxacin to elderly patients receiving theophylline was common and associated with a nearly twofold increase in the risk of hospitalization for theophylline toxicity. A similar risk was not observed with a neutral comparator group of antibiotics. When clinically appropriate, alternatives to ciprofloxacin should be considered for these patients when antibiotics are required. Alternatively, close monitoring for theophylline toxicity is warranted in cases where the use of ciprofloxacin is required.

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Appendix 1: Medications included in multivariable model

Medication use in 90 days preceding index date:

- CYP1A2 inhibitors: Allopurinol, Cimetidine, Disulfiram, Duloxetine, Ethinyl estradiol, Fluvoxamine, Isoniazid, Mefenamic acid, Mexiletine, Norfloxacin, Propafenone, Propranolol, Propylthiouracil, Riluzole, Rofecoxib, Ticlopidine
- CYP3A4 inhibitors: Amiodarone, Amprenavir, Aprepitant, Atazanavir, Clarithromycin, Darunavir, Delavirdine, Diltiazem, Erythromycin, Fluconazole, Fosamprenavir, Imatinib, Indinavir, Itraconazole, Lopinavir/ritonavir, Nefazodone, Nelfinavir, Ritonavir, Saquinavir, Telithromycin, Verapamil, Voriconazole
- CYP1A2/3A4 inducers: Amobarbital, Carbamazepine, Dexamethasone, Efavirenz, Etravirine, Nevirapine, Phenobarbital, Phenytoin, Pioglitazone, Primidone, Rifampin, Secobarbital

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