Analysis of Drug-Drug Interactions in Swiss Claims Data Using Tizanidine and Ciprofloxacin as a Prototypical Contraindicated Combination

Annika M. Jödicke, MSc[1,2] (iD), Ivanka Curkovic, MD[1,3], Urs Zellweger[4], Ivan T. Tomka, PhD[4], Thomas Neuer[1], Gerd A. Kullak-Ublick, MD[1], Malgorzata Roos, PhD[5], and Marco Egbring, MD[1,3] (iD)

Abstract

Background: Potential drug-drug interactions (pDDIs) are described in various case reports, but few studies have evaluated the impact of specific combinations on a population level. **Objective**: To analyze the type and frequency of multiple contraindicated (X-pDDIs) and major interactions (D-pDDIs) and to subsequently assess the impact of the particular combination of tizanidine and ciprofloxacin on outpatient physician visits and hospitalizations. **Methods:** Anonymized Swiss claims data from 524 797 patients in 2014-2015 were analyzed. First, frequencies of X- and D-pDDIs were calculated. Next, a retrospective cohort study was conducted among patients prescribed tizanidine and ciprofloxacin (exposed, n = 199) or tizanidine and other antibiotics (unexposed, n = 960). Hospitalizations and outpatient physician visits within 7, 14, and 30 days after initiation of antibiotic therapy were evaluated using multiple binary logistic regression and multiple linear regression. **Results:** The relative frequencies of X- and D-pDDIs were 0.4% and 6.65%, respectively. In the cohort study, significant associations between exposure to tizanidine and ciprofloxacin and outpatient physician visits were identified for 14 and 30 days (odds ratio [OR] = 1.61 [95% CI = 1.17-2.24], $P = 0.004$, and OR = 1.59 [95% CI = 1.1-2.34], $P = 0.016$). A trend for increased risk of hospitalization was found for all evaluated time periods (OR = 1.68 [95% CI = 0.84-3.17], OR = 1.52 [95% CI = 0.63-3.33], and OR = 2.19 [95% CI = 0.88-5.02]). **Conclusion and Relevance:** The interaction between tizanidine and ciprofloxacin is not only relevant for individual patients, but also at the population level. Further investigation of the impact of other clinically relevant DDIs is necessary to improve patient safety and reduce avoidable health care utilization.

Keywords

drug interactions, ciprofloxacin, muscle relaxants, drug safety, pharmacoepidemiology, health care utilization

Background

In recent decades, several reports have highlighted the importance of potential drug-drug interactions (pDDIs) as a risk factor for adverse drug events.[1,2] Nevertheless, the impact of DDIs on a public health level remains controversial: rates for hospitalizations attributable to DDIs vary between 0.1% and 6.2%, depending on study size and patient population.[3,4] Additionally, DDIs have been associated with increased length of stay and cost of hospitalization.[5] However, not all pDDIs are clinically relevant, and many can be managed safely.[6,7]

Although precautionary measures, such as DDI alert systems, are well established, coprescribing of drug combinations that potentially cause severe DDIs,[6-11] such as tizanidine and ciprofloxacin,[12] persists. Tizanidine is a central

α_2-adrenoceptor agonist with a narrow therapeutic range, which is approved in Switzerland for the treatment of spasticity.[13,14] Its metabolism is mainly mediated by cytochrome

[1]Department of Clinical Pharmacology and Toxicology, University Hospital Zurich and University of Zurich, Switzerland
[2]Swiss Federal Institute of Technology Zurich (ETH Zurich), Zurich, Switzerland
[3]EPha.ch AG, Project Drug Safety, Zurich, Switzerland
[4]Department of Client Services & Benefits, Helsana Group, Zurich, Switzerland
[5]EBPI, Department of Biostatistics, University of Zurich, Switzerland

Corresponding Author:
Marco Egbring, MD, Department of Clinical Pharmacology and Toxicology, University Hospital Zurich, University of Zurich, Raemistrasse 100, 8091 Zurich, Switzerland.
Email: marco.egbring@usz.ch

P450 1A2-isoenzyme. Ciprofloxacin, a quinolone antibiotic, has been shown to be a clinically relevant inhibitor of CYP1A2.[15] In a pharmacokinetic study, ciprofloxacin increased the area under the plasma-concentration curve of tizanidine by an average of 10-fold (range 6-fold to 24-fold).[15] Case reports highlight the potential threat to affected patients, with adverse reactions such as cardiovascular (eg, severe hypotension) and central nervous system (CNS)-depressive effects (eg, drowsiness) reported.[12,14-16] A recent analysis of the World Health Organization's database on adverse drug reactions (VigiBase™) identified 64 individual tizanidine-related cases involving ciprofloxacin, 4 of which had a fatal outcome.[17]

Objectives

This study comprised 2 parts. In the first explorative analysis, the frequency and type of different pDDIs occurring in Switzerland were established. Multiple interactions rated as contraindicated (X) or major (D) were investigated using a large claims database.

From this overview, we evaluated the risk of hospitalization and outpatient physician visits ("visits") associated with 1 contraindicated pDDI in the second part of the study. With respect to its contraindication, a relatively large number of patients were prescribed the combination of tizanidine and ciprofloxacin. Whereas the severity of the interaction has been well described in individual patients, its impact on the risk of hospitalization or visits has not yet been examined on a larger scale. Therefore, we selected this particular interaction for further evaluation.

Methods

Characteristics of the Study Population

Anonymized claims data was provided by a large health insurance company in Switzerland (Helsana Group). The data set encompassed 524 797 insured Swiss patients (age ≥ 18 years), accounting for 22 768 948 drug-prescriptions in 2014 and 2015. All participants were insured at the health insurance company for the entire course of the study, and no additional private insurance was allowed. All patients had at least 5 drug prescriptions within 1 calendar year. Participants who died within that period were excluded because legal requirements meant that the date of death was unavailable. The data set contained records of all health care invoices, information on prescribed drugs, health care utilization (eg, hospitalization, physician visits), demographic parameters, health insurance status, and costs for each patient.[18] The representativeness of the study population was also examined (Supplement 1; supplementary material available at http://journals.sagepub.com/home/aop/supplemental-data).

Ethical Approval

The harmlessness of the study was attested by the Cantonal Ethics Committee of Zurich, although no formal ethical approval was required under Swiss law. The concept of anonymization was approved by the Cantonal Data Security Officer.

Frequency and Type of Interactions

Potential DDIs were defined as the prescription of 2 drugs within a 7-day period. All combinations labeled "contraindicated" (X, n = 663) and "to be avoided" (D, n = 1785) in the Matrix database were evaluated (Supplement 2). Matrix is a DDI database from the Department of Clinical Pharmacology and Toxicology, University Hospital Zurich, Switzerland. Interactions are ranked by severity using a validated decision model, which has been described in detail elsewhere.[19] Frequency analyses were carried out for 2014 data, and stratification for age, sex, and number of different drugs was performed. Similar results were expected for 2015 data. Frequently implicated drug classes were described, and interactions were grouped with respect to the main potential (adverse) effect.

Interaction Between Tizanidine and Ciprofloxacin

Cohort Study Design. A cohort study was conducted with respect to hospitalizations and visits within 7, 14, and 30 days after starting antibiotic therapy in patients prescribed tizanidine between February 2014 and November 2015. The study design is illustrated in Figure 1. Exposed patients (ciprofloxacin and tizanidine, n = 199) were compared with a group of patients who were unexposed to ciprofloxacin (and, thus, to the ciprofloxacin-tizanidine interaction), but who were also prescribed tizanidine and a concomitant antibiotic with an antibiotic spectrum and indication comparable to those of ciprofloxacin (n = 960).

Definition of Exposed and Unexposed Patients. Exposure was predefined as the prescription of tizanidine and ciprofloxacin within the same 7-day period (n = 321). Among exposed patients, only those prescribed tizanidine before or on the same day as ciprofloxacin as the first occurrence were included. This definition was selected to increase the probability of concurrent exposure because the treatment duration of ciprofloxacin may vary with respect to the indication. Thus, potential cases may have been missed under this definition. If the drug combination was coprescribed within 7 days on multiple occasions for a patient during the study period, only the first occurrence of tizanidine-ciprofloxacin was evaluated (n = 231). The start date of ciprofloxacin was defined as the index date. To ensure comparability with the
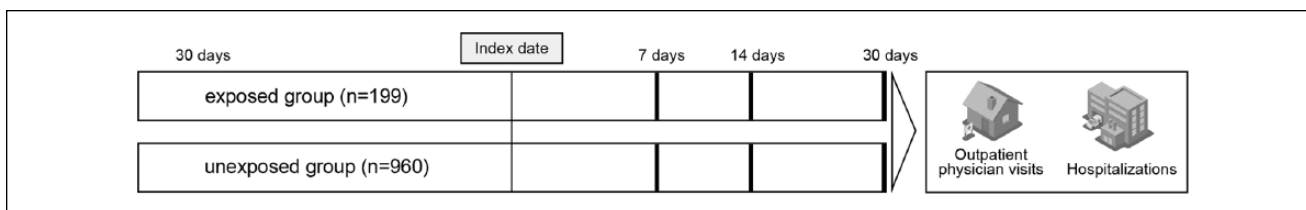
Figure 1. Cohort study design: Tizanidine patients were prescribed antibiotic therapy at the index date, with an exposed group prescribed ciprofloxacin and an unexposed group prescribed an antibiotic other than ciprofloxacin. Outcomes (outpatient physician visits, hospitalizations) were evaluated 7, 14, and 30 days after the index day.

unexposed group, patients prescribed ciprofloxacin in the 30 days prior to the index date were excluded, as were those prescribed any other antibiotic either at the index date or in the 7 days prior to the prescription of tizanidine. In total, data from 199 exposed patients were analyzed.

Unexposed patients were those prescribed tizanidine together with an antibiotic other than ciprofloxacin within the same 7-day period (n = 1422). Patients were included only if tizanidine was prescribed before or on the same day as the other antibiotic. If the drug combination was prescribed multiple times within separate 7-day periods for a patient during the study period, only the first occurrence of tizanidine-antibiotic (index date) was evaluated. Patients for whom a coprescription of antibiotic-tizanidine occurred in the 3 months prior to the index date were excluded. Patients prescribed more than 1 antibiotic at the index date or prescribed an antibiotic in the 7 days prior to the prescription of tizanidine were excluded, as were patients prescribed ciprofloxacin 30 days before or after the index date, to eliminate ciprofloxacin from the unexposed group. The final number of patients in the unexposed group was 960.

No additional restrictions regarding the prescription of either tizanidine or antibiotics before or after the index date were made in either group. No patients were prescribed either enoxacin or fluvoxamine, potent CYP1A2 inhibitors, in the 90 days before and 30 days after the index date. The patient inclusion process is displayed in a flowchart (Figure 2).

Investigated Outcomes. Both hospitalizations ("Hospitalization", binary) and visits ("Visits", binary and log[count]) were evaluated as adverse outcomes. Information on diagnoses for hospital admissions or reasons for visits were unavailable. Hospitalizations were identified using Swiss Diagnosis Related Group Codes, which are case-based lump sums used for the invoicing of inpatient hospitalization services.[20] Visits were identified using invoice codes for outpatient medical treatments,[21] and both visits at the physician's office and home visits by the physician were considered.

Statistical Methods. Data were analyzed using R (version 3.3.1). For dichotomous variables, absolute and relative

frequencies were calculated. For continuous variables, medians and interquartile ranges (IQRs) were provided. To identify associations between 2 discrete variables, the Fisher exact test was used. Associations between continuous and discrete variables with 2 levels were assessed using the Mann-Whitney test. Because the exposed patient group contained only 199 patients, age categories were transformed to a continuous variable by applying a stratified imputation. Multiple regression models adjusting for confounders were used to verify whether there was an association between the concurrent use of ciprofloxacin and tizanidine (exposed) and the baseline unexposed group with respect to the evaluated outcomes. Multiple logistic regression, adjusting for demographical variables, was applied for the binary outcomes of hospitalization or visit. Odds ratios were computed, and the number of visits was transformed logarithmically, with multiple linear regression adjusting for age, sex, and number of different drugs prescribed. Model selection was assisted by the Akaike information criterion. Power analysis was conducted using STATA (version 13.1, StataCorp LP). Values of $P < 0.05$ were considered statistically significant.

Results

Frequency and Type of Interactions

X-pDDIs were identified in 0.4% (n = 2119) of patients, and D-pDDIs were found in 6.65% (n = 34 885) of the study population (n = 524 797). Women were affected more frequently than men (X-pDDI: 0.34% for men, 0.45% for women; D-pDDI: 5.8% and 7.3%, respectively). The frequency of patients affected by interactions increased both with age (X-pDDI: 0.24% for age 25-34 years, 0.61% for age 75-84 years; D-pDDI 3.6% and 9.9%, respectively) and the number of different drugs prescribed per year (X-pDDI: 0.16% for 6-10 drugs, 1.67% for ≥16 drugs; D-pDDI 4.29% and 21.5%, respectively). Drug classes most frequently involved were propulsives (A03F, 16.5%), macrolides, lincosamides, and streptogramins (J01F, 13.9%) as well as antimycotics for systemic use (J02A, 8.3%) for X-interactions and NSAIDs (M01A, 17.4%), antithrombotic
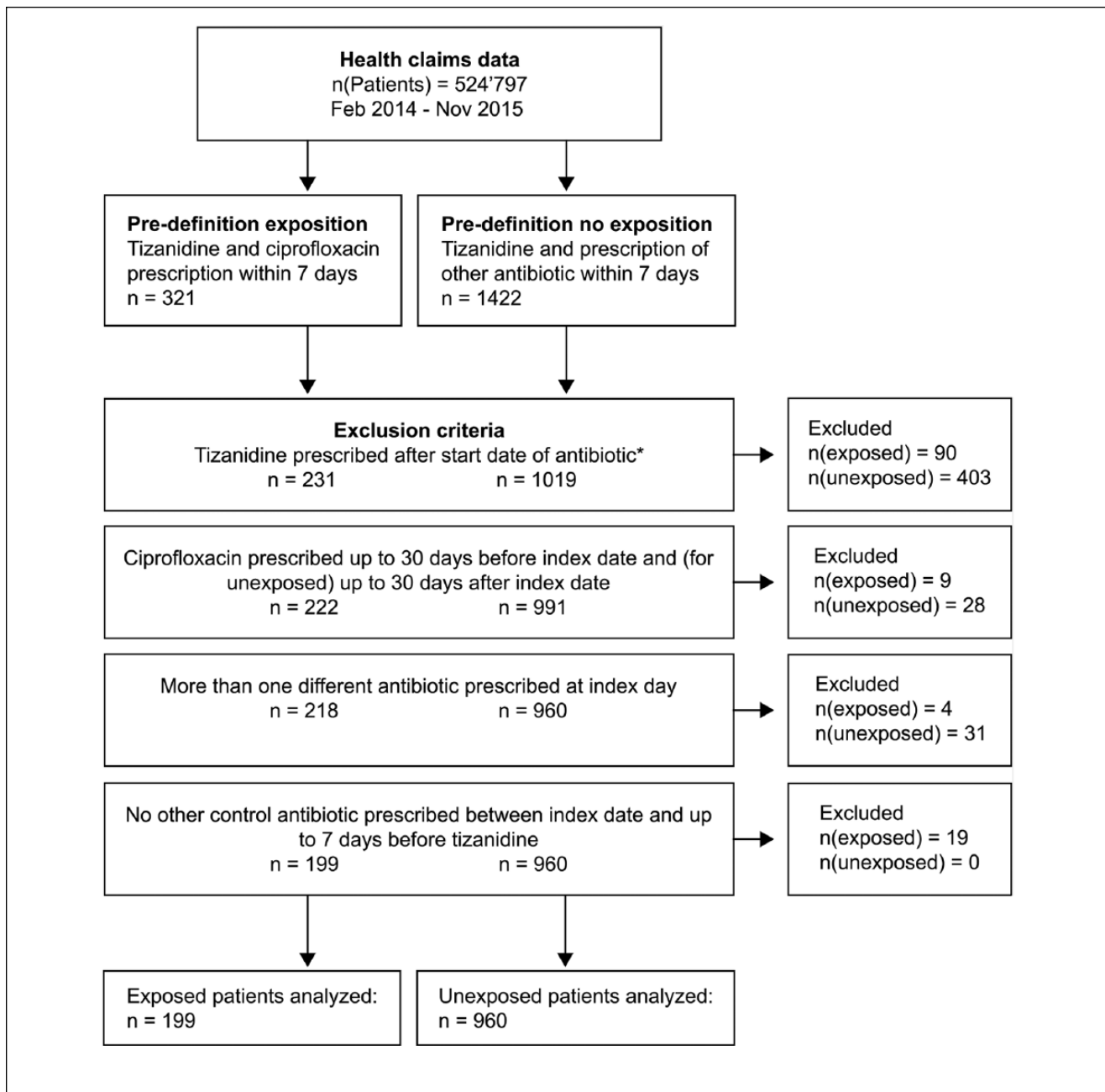
Figure 2. Inclusion of patients into the exposed and unexposed groups. Other antibiotics included penicillins with/without clavulanic acid, macrolides, fosfomycin, other fluoroquinolones, oral cephalosporins, sulfamethoxazole/trimethoprim, nitrofurantoin, and tetracyclines.
*Where an unexposed patient received the combination of an antibiotic prescribed within the 7-day period prior to tizanidine treatment, the combination must have been prescribed at least 3 months prior to the index date.

agents (B01A, 16.9%), and hypnotics/sedatives (N05C, 13.1%) for D-labeled interactions. The 5 most frequently contraindicated pDDIs in patients were domperidone/clarithromycin (n = 326), methotrexate/metamizole (n = 254), domperidone/fluconazole (n = 237), ciprofloxacin/tizanidine (n = 169), and clarithromycin/atorvastatin (n = 164).

When evaluated with respect to potential (adverse) effects of both X- and D-DDIs, highest frequencies among affected patients were found for interactions that increased risk of bleeding (n = 15 077, 32.7%), caused CNS-depressing effects (n = 11 847, 25.7%), and augmented the risk of cardiac toxicity (n = 9 798, 21.3%).

Table 1. Descriptive Statistics for Exposed (Ciprofloxacin and Tizanidine) and Unexposed (Other Antibiotic and Tizanidine) Groups.

	Exposed Group (n = 199)		Unexposed Group (n = 960)		
	Absolute Frequency	Relative Frequency	Absolute Frequency	Relative Frequency	P Value
Sex					
Male	66	33.2%	277	28.9%	0.23
Female	133	66.8%	683	71.1%	
Age					
Median	58.3		54.4		0.06
IQR	(46.5-69.4)		(41.8-68.2)		
Number of different drugs[a]					
Median	20		18		0.44
IQR	(13-26)		(12-27)		
Package strength tizanidine[b]					
2-mg Tablet	61	30.7%	296	30.8%	0.59
4-mg Tablet	114	57.3%	572	59.7%	
6-mg MR Capsule	23	11.6%	75	7.8%	
12-mg MR Capsule	—		7	0.7%	
Combination multiple strengths	1	0.5%	10	1.0%	

[a]Number of different drugs prescribed in the year of index date.
[b]Package(s) last prescribed before the index date.

Interaction Between Tizanidine and Ciprofloxacin

Descriptive statistics are summarized in Table 1. A noteworthy discrepancy between the groups was found for the age variable. The composition of antibiotic prescriptions received by unexposed patients at the index date involved multiple groups of antibacterials: penicillins with/without clavulanic acid (n = 354, 36.9%), macrolides (n = 154, 16%), fosfomycin (n = 145, 15.1%), other fluoroquinolones (n = 101, 10.5%), oral cephalosporins (n = 79, 8.2%), sulfamethoxazole/trimethoprim (n = 61, 6.4%), nitrofurantoin (n = 36, 3.8%), and tetracyclines (n = 30, 3.1%).

The risk of at least 1 visit after starting ciprofloxacin significantly increased at 30 and 14 days by as much as 1.6-fold. No significant association was found at 7 days. No relevant increase in the number of visits was identified for any of the 3 observation periods (Table 2).

Exposure to concomitant tizanidine and ciprofloxacin was associated with an increased risk of hospitalization within 7, 14, and 30 days after prescription of the antibiotic by 1.52- to 2.19-fold, respectively (statistically nonsignificant). A power analysis for the 30-day time frame (2-sample proportion tests corrected for allocation ratio [0.2070, n = 1159], significance level = 0.05) revealed a power of 0.44. This indicates that the study did not have sufficient power to detect a difference between the 2 groups with respect to hospitalization. No significant differences in the frequency of hospitalizations and visits at 7, 14, and 30 days before and after the index date were observed (data not shown).

Discussion

Our results illustrate the relevance of the interaction between tizanidine and ciprofloxacin on a public health level: this interaction was among the most frequent contraindicated interactions, and the probability of a visit increased significantly by 1.6-fold when tizanidine and ciprofloxacin were prescribed concomitantly at 30 and 14 days.

Interaction Between Tizanidine and Ciprofloxacin

Outpatient Physician Visits. Switzerland has approximately 6.7 million inhabitants older than 18 years, and approximately 239 000 of these have received tizanidine. Given the frequency of 0.58% for the ciprofloxacin-tizanidine interaction in tizanidine patients from our study population, we extrapolate that 1386 patients in Switzerland may be affected by this interaction annually. According to our findings, 64.8% of these patients would attend at least 1 visit within 14 days of treatment (n = 898). If this interaction could be avoided (unexposed patients: 52.9% visits), approximately 165 patients forgo the need for a visit.

Additional visits do not only have economic consequences: they ultimately indicate a medical condition. In contrast to hospitalizations, visits have rarely been studied as adverse outcomes in the literature. It can be assumed that, in many cases, patients may first contact their attending physician when they experience DDI-related adverse reactions or feel unwell during treatment rather

Table 2. Results of Multiple Logistic and Linear Regression Analysis for Hospitalizations and Outpatient Physician Visits.[a]

Outcome (Y)	Y = 1/n (Exposed; Unexposed)	Age	Sex, M	Number of Drugs	Exposure
Hospitalization (0/1) 30 Days					
β	13/199; 36/960	0.021	0.47	0.034	0.517
OR		1.02	1.6	1.03	1.68
95% CI (OR)		1.00-1.04	0.86-2.87	1.01-1.06	0.84-3.17
P Value		0.02	0.12	0.005	0.13
Hospitalization (0/1) 14 Days					
β	8/199; 24/960	0.017	0.543	0.037	0.422
OR		1.02	1.72	1.04	1.52
95% CI (OR)		0.995-1.04	0.81-3.52	1.01-1.07	0.63-3.33
P Value		0.13	0.14	0.01	0.32
Hospitalization (0/1) 7 Days					
β	8/199; 17/960	0.014	0.489	0.026	0.785
OR		1.01	1.63	1.03	2.19
95% CI (OR)		0.99-1.04	0.7-3.64	0.99-1.06	0.88-5.02
P Value		0.27	0.24	0.12	0.07
Visit (0/1) 30 Days					
β	155/199; 658/960	0.006	0.172	0.067	0.463
OR		1.01	1.19	1.07	1.59
95% CI (OR)		0.998-1.01	0.89-1.6	1.05-1.09	1.1-2.34
P Value		0.15	0.25	<0.001	0.016*
Visit (0/1) 14 Days					
β	129/199; 508/960	0.002	0.214	0.044	0.478
OR		1.00	1.24	1.05	1.61
95% CI (OR)		0.99-1.01	0.95-1.61	1.03-1.06	1.17-2.24
P Value		0.64	0.11	<0.001	0.004**
Visit (0/1) 7 Days					
β	80/199; 353/960	0.005	0.2	0.031	0.109
OR		1.00	1.22	1.03	1.12
95% CI (OR)		0.998-1.01	0.94-1.59	1.02-1.04	0.81-1.53
P Value		0.19	0.14	<0.001	0.50
Visit [log(count)] 30 days					
β		0.001	0.122	0.021	0.07
exp(β)		1.00	1.13	1.02	1.07
95%CI [exp(β)]		0.999-1.003	1.05-1.22	1.02-1.025	0.98-1.17
P Value		0.22	0.001	<0.001	0.13
Visit [log(count)] 14 Days					
β		0.0005	0.088	0.013	0.065
exp(β)		1.00	1.09	1.01	1.07
95%CI [exp(β)]		0.999-1.002	1.02-1.16	1.01-1.02	0.99-1.15
P Value		0.61	0.008	<0.001	0.10
Visit [log(count)] 7 Days					
β		0.0008	0.055	0.007	0.002
exp(β)		1.00	1.06	1.01	1.00
95% CI [exp(β)]		0.999-1.002	1.00-1.11	1.00-1.01	0.94-1.07
P Value		0.29	0.04	<0.001	0.96

Abbreviation: OR, odds ratio; Y = 1/n: Number of patients with hospitalization or visit in the exposed/unexposed group.
[a]*P < 0.05; **P < 0.01.

than requiring hospitalization; therefore, visits are of key importance when studying the impact of DDIs. Bourgeois et al[22] reported a significant trend of increased ADE-related visits to outpatient clinics in the United States, from 9.1 to 16.9 visits per 1000 persons between 1995 and 2005.[22] Emergency department visits have not been evaluated, because of low incidence. Fortunately, the ciprofloxacin-tizanidine interaction can be avoided: for several indications, ciprofloxacin can be replaced by another antibiotic that does not carry the same risk of a pharmacokinetic interaction. For tizanidine, pausing treatment during antibiotic therapy or drug substitution, depending on the patient's specific indication, are 2 options. As underlying medical conditions requiring tizanidine and acute antibiotic therapy are expected to increase the risk of hospitalizations and visits, confounding by indication was addressed by the inclusion of a control group (unexposed) who received antibiotics with a spectrum and indication comparable to that of ciprofloxacin. Cohort studies using a negative control precipitant are accepted study designs for the investigation of population health effects of pDDIs.[23]

Patients receiving several classes of oral antibiotics were combined to form an appropriate control group. Given the small number of patients receiving tizanidine and other quinolones, and the broader spectrum of indications for ciprofloxacin compared with other quinolones, a control group comprising only quinolones was not established.

Previous pharmacokinetic studies indicated a rapid increase in tizanidine exposure after the initiation of concomitant ciprofloxacin therapy, meaning that possible adverse reactions requiring health care utilization were expected to occur within a short time frame. Therefore, 7-, 14-, and 30-day periods were chosen, thus allowing for evaluation of the development of altered risk for adverse outcomes. Interestingly, the weakest association between exposure and visits was observed at 7 days (odds ratio = 1.12; 95% CI = 0.81-1.53), for reasons that remain speculative; overlapping effects of the underlying disease (antibiotic therapy) may have been more common in the initial treatment period. Additionally, severe adverse reactions in susceptible patients may have appeared rapidly, possibly requiring hospitalization rather than a visit.

Hospitalization. The 2.19-fold increased risk of hospitalization (95% CI = 0.88-5.02; P = 0.07) shortly after the start of ciprofloxacin therapy in patients receiving tizanidine indicates a problematic trend. As expected, the highest risk of hospitalization was observed within 7 days of concomitant treatment. The clinical relevance of other pDDIs was evaluated for different combinations, including statins/macrolides and levothyroxine/warfarin. Whereas some studies found an increased risk of hospitalizations,[24-27] others could not demonstrate an association.[28]

Frequency and Type of Interactions

We found an overall frequency of contraindicated interactions of 0.4% and a considerably higher rate of 6.65% among patients prescribed at least 1 major drug combination (n = 524 797). Such high rates of severe interactions highlight the need for ongoing implementation of DDI-alerting systems to prevent the prescription of potentially harmful combinations.

The frequency of interactions has been analyzed in several studies and has depended on the type of interaction studied, the definition of interactions, the study setting (eg, claims data, clinical study), and the patient population.[11] An analysis of contraindicated pDDIs in Swiss claims data with a focus on the specialization of physicians causing the pDDI using the defined daily-dose method revealed rates (0.4% in female and 0.5% in male patients)[29] similar to that in our study. We, therefore, consider our use of a 7-day time frame to be a pragmatic and reasonable method to estimate the overall frequencies of multiple pDDIs in large data sets.

Time frame methods are commonly used in the literature to identify pDDIs.[8,9,11,30] We opted for a short time frame of 7 days to increase the probability of concomitant intake. In line with findings from other claims data-based studies,[8-11] we identified higher frequencies of pDDIs associated with female gender, increasing age, and number of different drugs. Because the study population was older and included a higher proportion of female patients compared with the general Swiss population (Supplement 1), the frequencies of pDDIs may be overestimated when generalized to Switzerland. The most frequent possible adverse effects of pDDIs in our study were the risk of bleeding, CNS depression, and cardiac toxicity, which was comparable with previous findings.[8,9]

Limitations

This study has several limitations. Calculations were performed under the assumption of immediate intake of the prescribed drugs. Because there can be no certainty of actual drug intake, all interactions were referred to as "potential" DDIs. Formally contraindicated combinations may be prescribed intentionally as off-label treatment in exceptional cases. Information on over-the-counter medication and prescriptions during hospitalization was lacking in the data set. As interactions involving such medications could not be taken into account, the frequency of interactions may be underestimated. As of the conservative approach of using a 7-day time frame to define pDDI, the frequency of pDDIs may have been underestimated, especially where pDDIs between continuous therapy and acute prescription may have been missed.

Regarding the cohort study, susceptibility to confounding by indication was reduced by using a comparable control

group, but it might not have been eliminated completely. Patterns of antibiotic use for certain indications may vary, and the need for physician visits may be associated with the severity of infection. No diagnoses describing the indications for antibiotic therapy were available in the data set. Differences between the groups regarding unmeasured covariates (eg, comorbidities, prior health care utilization, smoking status) cannot be ruled out.

Furthermore, information on the actual admission diagnoses for hospitalization or reasons for visits was unavailable. Finally, the increased risk of hospitalization and visits compared with the control group is believed to be largely attributable to ciprofloxacin, thus suggesting an impact of the interaction. However, no causal relationship can be established.

Conclusion and Relevance

The example of concomitant tizanidine and ciprofloxacin treatment illustrates that severe DDIs are not only critical for individual patients, but may also be relevant on a public health level by increasing the risk of health care utilization. Because this interaction can be prevented by therapy adjustment, adverse outcomes can be avoided. With societies growing older and rising numbers of patients experiencing multimorbidity and polypharmacy, evaluating the impact of DDIs from a public health perspective is of increasing importance to reduce avoidable health care utilization.

ORCID iDs

Annika M. Jödicke [iD] https://orcid.org/0000-0002-0000-0110
Marco Egbring [iD] https://orcid.org/0000-0002-4201-1483

References

1. Gnjidic D, Johnell K. Clinical implications from drug-drug and drug-disease interactions in older people. *Clin Exp Pharmacol Physiol*. 2013;40:320-325.

2. Leone R, Magro L, Moretti U, et al. Identifying adverse drug reactions associated with drug-drug interactions: data mining of a spontaneous reporting database in Italy. *Drug Saf*. 2010;33:667-675.

3. Becker ML, Kallewaard M, Caspers PW, Visser LE, Leufkens HG, Stricker BH. Hospitalisations and emergency department visits due to drug-drug interactions: a literature review. *Pharmacoepidemiol Drug Saf*. 2007;16:641-651. doi:10.1002/pds.1351

4. Dechanont S, Maphanta S, Butthum B, Kongkaew C. Hospital admissions/visits associated with drug-drug interactions: a systematic review and meta-analysis. *Pharmacoepidemiol Drug Saf*. 2014;23:489-497. doi:10.1002/pds.3592

5. Moura C, Acurcio F, Belo N. Drug-drug interactions associated with length of stay and cost of hospitalization. *J Pharm Pharm Sci*. 2009;12:266-272.

6. Solberg L, Hurley J, Roberts M, et al. Measuring patient safety in ambulatory care: potential for identifying medical group drug–drug interaction rates using claims data. *Am J Manag Care*. 2004;10(11, pt 1):753-759.

7. Aparasu R, Baer R, Aparasu A. Clinically important potential drug-drug interactions in outpatient settings. *Res Social Adm Pharm*. 2007;3:426-437. doi:10.1016/j.sapharm.2006.12.002

8. Jazbar J, Locatelli I, Horvat N, Kos M. Clinically relevant potential drug-drug interactions among outpatients: A nationwide database study. *Res Social Adm Pharm*. 2018;14(6):572-580. doi:10.1016/j.sapharm.2017.07.004

9. Holm J, Eiermann B, Eliasson E, Mannheimer B. A limited number of prescribed drugs account for the great majority of drug-drug interactions. *Eur J Clin Pharmacol*. 2014;70:1375-1383. doi:10.1007/s00228-014-1745-3

10. Bjerrum L, Andersen M, Petersen G, Kragstrup J. Exposure to potential drug interactions in primary health care. *Scand J Prim Health Care*. 2003;21:153-158.

11. Malone DC, Hutchins DS, Haupert H, et al. Assessment of potential drug-drug interactions with a prescription claims database. *Am J Health Syst Pharm*. 2005;62:1983-1991.

12. Momo K, Homma M, Kohda Y, Ohkoshi N, Yoshizawa T, Tamaoka A. Drug interaction of tizanidine and ciprofloxacin: case report. *Clin Pharmacol Ther*. 2006;80:717-719.

13. Sirdalud/Sirdalud MR (tizanidine) [product information]. Novartis Pharma Schweiz AG, Risch Switzerland; 2017.

14. Henney HR III, Runyan JD. A clinically relevant review of tizanidine hydrochloride dose relationships to pharmacokinetics, drug safety and effectiveness in healthy subjects and patients. *Int J Clin Pract*. 2008;62:314-324. doi:10.1111/j.1742-1241.2007.01660.x

15. Granfors MT, Backman JT, Neuvonen M, Neuvonen PJ. Ciprofloxacin greatly increases concentrations and hypotensive effect of tizanidine by inhibiting its cytochrome P450 1A2-mediated presystemic metabolism. *Clin Pharmacol Ther*. 2004;76:598-606. doi:10.1016/j.clpt.2004.08.018

16. Abd-Elsayed A, Elsharkawy H, Sakr W. A severe interaction between tizanidine and ciprofloxacin. *J Clin Anesth*. 2015;27:698. doi:10.1016/j.jclinane.2015.05.016

17. Dahmke H, Jetter A, Kupferschmidt H, Kullak-Ublick G, Weiler S. Co-administration of tizanidine and ciprofloxacin:

a retrospective analysis of the WHO pharmacovigilance database [abstract]. *Clin Ther*. 2017;39(8).

18. Wertli MM, Reich O, Signorell A, Burgstaller JM, Steurer J, Held U. Changes over time in prescription practices of pain medications in Switzerland between 2006 and 2013: an analysis of insurance claims. *BMC Health Serv Res*. 2017;17:167. doi:10.1186/s12913-017-2086-6

19. Far E, Curkovic I, Byrne K, et al. Validation of a transparent decision model to rate drug interactions. *BMC Clin Pharmacol Toxicol*. 2012;13:7.

20. SwissDRG AG. SwissDRG. https://www.swissdrg.org/de/akutsomatik/swissdrg. Accessed December 5, 2017.

21. FMH. TARMED Ambulante Tarife. https://www.fmh.ch/ambulante_tarife.html. Accessed December 5, 2017.

22. Bourgeois FT, Shannon MW, Valim C, Mandl KD. Adverse drug events in the outpatient setting: an 11-year national analysis. *Pharmacoepidemiol Drug Saf*. 2010;19:901-910.

23. Hennessy S, Leonard CE, Gagne JJ, et al. Pharmacoepidemiologic methods for studying the health effects of drug-drug interactions. *Clin Pharmacol Ther*. 2016;99:92-100. doi:10.1002/cpt.277

24. Patel AM, Shariff S, Bailey DG, et al. Statin toxicity from macrolide antibiotic coprescription. *Ann Intern Med*. 2013;158:869-876.

25. Wright AJ, Gomes T, Mamdani MM, Horn JR, Juurlink DN. The risk of hypotension following co-prescription of macrolide antibiotics and calcium-channel blockers. *CMAJ*. 2011;183:303-307.

26. Pincus D, Gomes T, Hellings C, et al. A population-based assessment of the drug interaction between levothyroxine and warfarin. *Clin Pharmacol Ther*. 2012;92:766-770.

27. Hamilton R, Briceland L, Andritz M. Frequency of hospitalization after exposure to known drug-drug interactions in a Medicaid population. *Pharmacotherapy*. 1998;18:1112-1120.

28. Mesgarpour B, Gouya G, Herkner H, Reichardt B, Wolzt M. A population-based analysis of the risk of drug interaction between clarithromycin and statins for hospitalisation or death. *Lipids Health Dis*. 2015;14:131.

29. Bucher HC, Achermann R, Stohler N, Meier CR. Surveillance of physicians causing potential drug-drug interactions in ambulatory care: a pilot study in Switzerland. *PLoS One*. 2016;11:e0147606. doi:10.1371/journal.pone.0147606

30. Ostermann JK, Berghöfer A, Andersohn F, Fischer F. Frequency and clinical relevance of potential cytochrome P450 drug interactions in a psychiatric patient population—an analysis based on German insurance claims data. *BMC Health Serv Res*. 2016;16:482. doi:10.1186/s12913-016-1724-8