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BRIEF REPORT

# Potentially Serious Drug Interactions Resulting From the Pretravel Health Encounter

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Travelers seen for pretravel health encounters are frequently prescribed new travel-related medications, which may interact with their previously prescribed medications. In a cohort of 76 324 travelers seen at 23 US clinics, we found that 2650 (3.5%) travelers were prescribed travel-related medications with potential for serious drug interactions.

**Keywords.** drug interactions; pretravel health care; travel medicine.

US travelers made 80 million international trips during 2016 [1]. An increasing number of travelers are elderly or have medical comorbidities [2–5]. The US Centers for Disease Control and Prevention (CDC) recommends that individuals traveling internationally seek medical advice before their trip. At pretravel medical encounters, travel-related medications may be prescribed for prophylaxis or empiric self-treatment of travel-related illnesses, such as malaria, travelers' diarrhea, or altitude illness. The prescribing of travel-related medications in patients taking medications for preexisting conditions poses a risk for drug-drug interactions (DDIs). The US cost of drug-related morbidity and mortality has been estimated to be upwards of $400 billion dollars [6, 7]; although the incidence of drug interactions varies widely, they are recognized as clinically significant causes of drug-related morbidity, especially in elderly patients [8, 9], and are receiving increasing national scrutiny for their importance and preventability.

Limited data are available on the prevalence of drug interactions relating to the pretravel health encounter. In a retrospective cohort study conducted in Israel, investigators identified potential interactions in 22% of patients with chronic medical conditions who were prescribed travel-related medications, with fluoroquinolones and azithromycin being the most commonly implicated [5]. We were therefore interested in evaluating the potential side effects of new drug interactions with preexisting medications in US residents traveling abroad. To perform this study, we used data available through the CDC-supported Global TravEpiNet (GTEN) national consortium.

## METHODS

### Study Population

GTEN is a consortium of US clinical practices that provide pretravel health care to international travelers, with sites geographically distributed across the United States. We evaluated data for international travelers seen at 23 GTEN sites from July 1, 2009, through December 31, 2015. For the purposes of this study, for each clinic visit associated with a unique itinerary, travelers used a secure web-based structured questionnaire to provide details about their medical history, preexisting medications, and travel itinerary. Clinicians verified the information provided by travelers and entered additional data about vaccinations administered and medications prescribed during the pretravel encounter. An institutional review board at each participating site either approved or exempted the study.

### Identification of Potential Drug Interactions

We compiled all preexisting medications of travelers in the study population and included for analysis only those medications reported by >10 travelers. Two pharmacists (B.B. and R.B.) examined the list of previously prescribed medications and identified potentially serious drug interactions with travel-related medications based on Micromedex-indexed drug interactions (Truven Health Analytics, Inc., Ann Arbor, MI).

### Clinical Significance of Drug Interactions

To evaluate the clinical significance of drug interactions, each interaction was classified according to the (1) clinical effect of interaction, (2) severity of interaction, (3) quality of published evidence indicating that the drug interaction can cause an adverse drug event (ADE), and (4) frequency of concomitant prescriptions for the drug interaction in our study population. Published evidence for interactions was identified using the

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medication name and class of interaction as PubMed search terms. The same 2 pharmacists used a structured assessment procedure formulated by the Netherlands Working Group on Pharmacotherapy and Drug Information to separate classes of interactions into a 6-point scale based upon the assessor's judgment of level of severity and a 5-point quality of evidence scale [10].

## RESULTS

We evaluated a total of 76 324 GTEN clinical encounters during the study period. Overall, potential interactions were identified in 2650 (3.5%) travelers. Of travelers with potential interactions, the median age was 55 years, with 61% being older than age 50 years. Fifty-six percent of travelers were female, and 92% had at least 1 medical condition, with 41% having at least 3 comorbid conditions. The majority (54%) traveled for 14 days or less, 66% traveled for leisure purposes, and 75% traveled to a country of low/medium human development.

Of the >200 preexisting medications that were reported by >10 travelers, 11 were determined to exhibit more clinically relevant potential interactions with travel-related medications; these included selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), trazodone, warfarin, methotrexate, simvastatin, hydroxychloroquine, and dextroamphetamine/amphetamine (Table 1). The severity of the identified potential interactions was high, with 24/29 interactions identified as potentially life-threatening (E–F severity), 4/29 as clinically significant based upon patient risk factors (C–D severity), and 1/29 as having a minimal adverse effect profile (A–B severity). However, of interactions identified as potentially life-threatening, 22/24 of these drug–drug interactions were identified as mechanistic based on additive effects from QTc prolongation without further published evidence to delineate the cumulative interaction risk. Overall, the quality of the literature supporting the identified potential interactions was minimal, with literature support for 7/29 interactions.

The single most common potential interaction was between ciprofloxacin and simvastatin, accounting for up to 33% of all possible interactions, with potential to cause rhabdomyolysis (Table 1). Also notable were the interactions between ciprofloxacin or azithromycin and the SSRIs, with potential to cause QTc prolongation, responsible for >35% of potential interactions. Lastly, prescription of azithromycin, ciprofloxacin, or atovaquone-proguanil in patients on warfarin, with potential to cause an increased international normalized ratio (INR), was found to be responsible for approximately 10% of total potentially serious interactions.

## DISCUSSION

Pretravel health care includes the administration of routine and destination-specific immunizations, as well as the prescription of travel-related medications. Given the increasing numbers of international travelers with medical comorbidities, there is a greater potential for drug interactions to arise from the pretravel encounter. In this study, we identified potentially serious drug interactions between travelers' previously presecribed medications and newly prescribed travel-related medications in a small but clinically relevant proportion of those presenting for pretravel health care at a network of US travel clinics.

Potential drug interactions identified were between the travel-related medications ciprofloxacin, azithromycin, atovaquone-proguanil, chloroquine, and mefloquine, and the previously prescribed medications citalopram, escitalopram, fluoxetine, simvastatin, and warfarin. Simvastatin, an HMG-CoA reductase inhibitor commonly used for dyslipidemia, is metabolized by the cytochrome P450 3A4 enzyme system. Ciprofloxacin is a weak CYP3A4 inhibitor, and its concurrent use with simvastatin can increase the risk of rhabdomyolysis and myopathy. Although a similar interaction may occur between ciprofloxacin and other HMG-CoA reductase inhibitors that are major CYP3A4 substrates such as atorvastatin and lovastatin, such interactions are poorly described in the literature and were not considered as potential drug interactions in this study.

Concurrent use of azithromycin, ciprofloxacin, or atovaquone-proguanil with warfarin can increase previously therapeutic INR levels and lead to serious bleeding events [11]. Azithromycin and ciprofloxacin disrupt vitamin K production in the gut, whereas atovaquone displaces warfarin from plasma proteins. In the case of atovaquone-proguanil, prescribed for malaria chemoprophylaxis, bleeding risk can be mitigated by starting the regimen in advance of travel and adjusting the warfarin dose according to measured INR effects. In contrast, as ciprofloxacin and azithromycin are prescribed for self-treatment of traveler's diarrhea, their effect on INR during an episode of diarrhea is difficult to predict. Unfortunately, alternative therapies for traveler's diarrhea, such as rifaximin and bismuth, also have potential to increase INR.

The potential for QTc prolongation due to interactions between antibiotics and antidepressants was among the most frequently identified side effects in our study. QTc prolongation has the potential to result in cardiac arrhythmias, including death. To date, there has not been an appreciable evaluation of the significance of QTc prolongation on patient outcomes in a general population, and the degree to which 1 medication may prolong the QTc interval relative to another is not always clear or comparable. The challenge in assessing drug interactions with this potential ADE is the lack of patient-specific information to allow for risk stratification, which may include a patient's cardiac history and comorbidities, baseline QTc, or additional medications that would additively prolong the QTc [12]. Notably, the occurrence of travelers' diarrhea, which would be the indication for use of ciprofloxacin and azithromycin, is complicated by the potential for electrolyte imbalances due to losses through the gastrointestinal tract [13]. Despite this

**Table 1. Potential Drug Interactions Among 2650 International Travelers Presenting to a Consortium of US Clinical Practices for Pretravel Health Care**

| Medication Interaction | No. (% of All Potential Interactions) | Clinical Effect | Mechanism | Severity[a] | Quality of Evidence[b] |
|---|---|---|---|---|---|
| Acetazolamide | | | | | |
| Dextroamphetamine | 38 (1.4) | Amphetamine toxicity | Decreased amphetamine elimination with urine alkalization | C | - |
| Ciprofloxacin | | | | | |
| Citalopram | 371 (14.0) | QTc prolongation | QTc prolongation | E | - |
| Escitalopram | 278 (10.5) | QTc prolongation | QTc prolongation | E | - |
| Fluoxetine | 361 (13.6) | QTc prolongation | QTc prolongation | E | - |
| Nortriptyline | 40 (1.5) | QTc prolongation | QTc prolongation | E | - |
| Amitriptyline | 51 (1.9) | QTc prolongation | QTc prolongation | E | - |
| Trazodone | 178 (6.7) | QTc prolongation | QTc prolongation | E | - |
| Warfarin | 125 (4.7) | Increased INR | Vitamin K production disrupted in gut | C | 4 |
| Hydroxychloroquine | 26 (1.0) | QTc prolongation | QTc prolongation | E | - |
| Simvastatin | 969 (36.6) | Rhabdomyolysis | Weak CYP 3A4 inhibition | E | 1 |
| Azithromycin | | | | | |
| Citalopram | 17 (0.6) | QTc prolongation | QTc prolongation | E | - |
| Escitalopram | 10 (0.4) | QTc prolongation | QTc prolongation | E | - |
| Fluoxetine | 10 (0.4) | QTc prolongation | QTc prolongation | E | - |
| Nortriptyline | 3 (0.1) | QTc prolongation | QTc prolongation | E | - |
| Amitriptyline | 2 (0.1) | QTc prolongation | QTc prolongation | E | - |
| Trazodone | 6 (0.2) | QTc prolongation | QTc prolongation | E | - |
| Warfarin | 10 (0.4) | Increased INR | Vitamin K production disrupted in gut | A | 3 |
| Hydroxychloroquine | 2 (0.1) | QTc prolongation | QTc prolongation | E | - |
| Simvastatin | 44 (1.7) | Rhabdomyolysis | None identified | E | 2 |
| Atovaquone-proguanil | | | | | |
| Warfarin | 146 (5.5) | Increased INR | Competitive plasma protein displacement | C | 1 |
| Doxycycline | | | | | |
| Methotrexate | 5 (0.2) | Methotrexate toxicity | Competitive plasma protein displacement | D | 1 |
| Chloroquine/mefloquine | | | | | |
| Citalopram | 42 (1.6) | QTc prolongation | QTc prolongation | E | - |
| Escitalopram | 24 (0.9) | QTc prolongation | QTc prolongation | E | - |
| Fluoxetine | 47 (1.8) | QTc prolongation | QTc prolongation | E | - |
| Nortriptyline | 23 (0.9) | QTc prolongation | QTc prolongation | E | - |
| Amitriptyline | 5 (0.2) | QTc prolongation | QTc prolongation | E | 0 |
| Trazodone | 17 (0.6) | QTc prolongation | QTc prolongation | E | - |
| Azithromycin | 88 (3.3) | QTc prolongation | QTc prolongation | E | - |
| Hydroxychloroquine | 1 (0) | QTc prolongation | QTc prolongation | E | - |

Level of evidence is according to the Netherlands Working Group on Pharmacotherapy and Drug Information [10].

Abbreviations: INR, international normalized ratio; QTc, .

[a]The severity scale was classified alphabetically (A–F) with increasing significance: A–B interactions demonstrate minimal clinical relevance. C–D interactions show clinical relevance but are largely dependent on patient risk factors. E–F interactions are potentially life-threatening.

[b]The numeric (0–4) quality of evidence scale distinguished theoretical interactions from clinically proven effects: (-) Theoretical drug interaction without published supporting evidence; (0) in vitro or animal studies; (1) case reports without clearly demonstrated interaction causal effect; (2) case reports with clearly demonstrated interaction causal effects or case series; (3) controlled interaction studies with surrogate effects; (4) controlled interaction studies with relevant effects. If a drug interaction combination had more than 1 published interaction study, the study with the highest identified quality rating was documented.

potential risk, however, there is a lack of documented reports of sudden cardiac death or arrhythmias attributed to this DDI, and thus the clinical actionability is unclear.

We were able to identify potentially clinically significant DDIs with commonly prescribed medications among a large cohort of US travelers; however, there were a number of limitations to this study. First, we did not evaluate the clinical outcomes associated with the drug interactions identified, so the implications on patient outcomes are unclear. Second, our quality of evidence assessment of drug interactions depended on published literature to define the interaction mechanism, clinical effect, and likelihood of the drug interaction causing the identified adverse event. This is problematic as there are few published data on specific drug interactions with respect to

their clinical significance. Many of the identified travel medication interactions are based on what is listed in the drug label or drug compendia. Third, we identified drug interaction significance regardless of patient-specific characteristics, frequency of adverse events experienced from the interactions, medication dosing frequency or duration, or in some cases the clinical degree of the listed adverse event. Fourth, our analysis is limited to those medications prescribed by health care providers, and thus interactions of over-the-counter medications, such as loperamide, were not evaluated. Finally, we classified QTc prolongation identically for the different medications with this interaction and were not able to adjust for the potential differences in effect that might be caused by each of the medications.

ADEs resulting from DDIs can be prevented by careful review of medications and potential interactions at the time of prescribing new travel-related medications. Challenges in acquiring complete and accurate medication lists, identifying potential DDIs, and determining a patient's clinical risk related to a DDI have kept ADEs secondary to drug–drug interactions a concern. Strategies to mitigate ADEs from DDIs include electronic prescribing with drug interaction alert software, good clinical practice through optimal medication prescribing, and multidisciplinary educational strategies to unmask potential DDIs. Our study highlights the frequency of potential interactions and the importance of identifying them through careful review of previously prescribed medications. Additional studies are needed to optimize resources aimed at reducing the incidence of ADE-related DDIs.


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