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Original Contribution

CYP2C19 drug-drug and drug-gene interactions in ED patients☆,☆☆,★

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ABSTRACT

Background: CYP450 polymorphisms result in variable rates of drug metabolism. CYP drug-drug interactions can contribute to altered drug effectiveness and safety.
Study objectives: The primary objective was to determine the percentage of emergency department (ED) patients with cytochrome 2C19 (CYP2C19) drug-drug interactions. The secondary objective was to determine the prevalence of CYP2C19 polymorphisms in a US ED population.
Methods: We conducted a prospective observational study in an urban academic ED with 72,000 annual visits. Drug ingestion histories for the 48 hours preceding ED visit were obtained; each drug was coded as CYP2C19 substrate, inhibitor, inducer, or not CYP2C19 dependent. Ten percent of patients were randomized to undergo CYP2C19 genotyping using the Roche Amplichip.
Results: A total of 502 patients were included; 61% were female, 65% were white, and median age was 39 years (interquartile range, 22-53). One hundred thirty-one (26.1%) patients had taken at least 1 CYP2C19-dependent home drug. Eighteen (13.7%) patients who were already taking a CYP2C19-dependent drug were given or prescribed a CYP2C19-dependent drug while in the ED. Among the 53 patients genotyped, 52 (98%) were extensive metabolizers and 1 was a poor metabolizer.
Conclusions: In a population of ED patients, more than a quarter had taken a CYP2C19-dependent drug in the preceding 48 hours, but few were given or prescribed another CYP2C19-dependent drug in the ED. On genotyping analysis, CYP2C19 polymorphisms were uncommon in our cohort. We conclude that changing prescribing practice due to CYP2C19 drug-drug interaction or genotype is unlikely to be useful in most US ED populations.

1. Introduction

Cytochrome P450 (CYP450) polymorphisms result in variable rates of drug metabolism. This has important implications for drug effectiveness and safety [1]. Hepatic cytochrome 2C19 (CYP2C19), a CYP450 subtype, metabolizes up to 15% of known pharmaceuticals [2] including drugs with narrow therapeutic windows frequently encountered by physicians such as warfarin, clopidogrel, and carbamazepine (Table 1). CYP2C19 enzyme phenotypes are classified as poor metabolizer, intermediate metabolizer, extensive (normal) metabolizer, and ultrarapid metabolizer depending upon the patient's underlying genetic polymorphisms [3]. Commercially available genotype assays identify poor metabolizers and extensive metabolizers through identification of a variable number of gene polymorphisms [4].

Genotyping for specific polymorphisms is increasingly recommended by the Food and Drug Administration before instituting drug therapy [5]. There are a number of drugs where genotyping can predict adverse drug events, drug effectiveness, or therapeutic failure [6]. These drugs include abacavir [7,8], clopidogrel [9], and tamoxifen [10]. In addition, genotyping for glucose-6-phosphate deficiency before prescribing of certain hemolytic drugs is advised [11,12]. The National Comprehensive Cancer Network recommends genotyping for certain tumor genes associated with improved chemotherapeutic efficacy before initiation of therapy [13]. Knowledge of patient genotypes in the emergency department (ED) may lead to improved efficacy and safety of drugs prescribed in the near future. However, genotyping is not sufficient to predict safety and effectiveness [14], and accounting for clinical factors such as drug-drug interaction may be equally important [1,15]. Therefore, characterizing the frequency of drug-drug interactions and the prevalence of

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Table 1
CYP2C19-dependent drugs used in EDs

Drug/drug class	Related emergency condition	Role of CYP2C19
Warfarin	Venous thrombosis, pulmonary embolism, atrial fibrillation	Primarily metabolized by CYP2C9, although inhibition of CYP2C19 may result in elevated INR.
Clopidogrel	Acute coronary syndrome, myocardial infarction, recent stroke	Dependent on CYP2C19 for conversion to active metabolite.
Proton pump inhibitors (PPIs): esomeprazole, lansoprazole, omeprazole, pantoprazole	Ulcers, gastroesophageal reflux disease	Most PPIs are inhibitors of CYP2C19 which can affect effectiveness of concurrently administered CYP2C19-dependent drugs.
Antiepileptics: diazepam, phenytoin, *S*-mephenytoin, phenobarbitone, oxcarbazepine	Epilepsy, other seizure disorders	Inhibition of CYP2C19 may lead to antiepileptic toxicity.
Antimicrobials: isoniazid, voriconazole	Bacterial or fungal infection	Isoniazid is an inhibitor of CYP2C19 which can affect effectiveness of concurrently administered CYP2C19-dependent drugs.
Antidepressants: citalopram, amitriptyline	Depression, anxiety, and other psychological disorders	Inhibition of this enzyme may lead to serotonin or cardiovascular toxicity due to excess parent drug.

genetic polymorphisms in an ED population allows for an estimation of the implications for drug-gene interaction in ED patients [1,16].

Drug-gene interactions are especially important with the CYP2C19 enzyme which is responsible for metabolism of many clinically pertinent drugs in the ED. Pharmacokinetic differences have been demonstrated between CYP2C19 genotype subgroups for several drugs [3] including proton pump inhibitors [17], sedatives [18], anticonvulsants [19], antidepressants [20], and antimicrobials [21,22]. Metabolism of these drugs varies considerably from extensive metabolizers to poor metabolizers. Poor metabolizer prevalence varies by race. A total of 12%-23% of Asians [23–25], 1%-6% of whites [26–28], and 1%-7.5% of Africans [29] are classified as CYP2C19 poor metabolizers. Identification of drug-gene and pairing this information with drug-drug interaction data may alter the way ED physicians prescribe CYP2C19-dependent drugs. We have chosen to focus on CYP2C19 because of the high potential for interactions with narrow therapeutic drugs. In addition, many of these drugs are metabolized almost exclusively through this pathway, with no redundancy, raising the potential for clinically significant interactions. The primary objective was to determine the percentage of ED patients with CYP2C19 drug-drug interactions. The secondary objectives were to determine the prevalence of CYP2C19 polymorphisms in a US ED population and to determine if genotyping and identification of drug-drug interactions for CYP2C19 could reasonably alter drug therapy by ED physicians.

2. Materials and methods

2.1. Patients and study design

This was a prospective observational cohort gathered in a large urban academic US ED with approximately 72,000 patient visits per year. The study enrollment procedures are described in the parent trial (Clinical Trials # NCT01859715) [15]. In brief, subjects were included if they self-reported pain or nausea during the initial nursing assessment. Patients were excluded if they were younger than 18 years, unable to speak English, or previously diagnosed with chronic pain or cyclic vomiting. In addition, those with measured or known glomerular filtration rate of <60 mL/(min 1.73 m^2) or those with acute altered mental status were excluded. In patients with dementia or critical illness, the drug ingestion history was reconciled with the health care proxy. Patients were approached after triage, after nurse drug reconciliation, and after initial stabilization when the patient arrived by ambulance. The local institutional review board approved the study, and all subjects provided written informed consent.

2.2. Drug ingestion histories

Detailed drug histories for the 48 hours preceding the ED visit were obtained by the principal investigator or a professional research assistant (JC) trained in identical methods. All prescription drugs, nonprescription drugs, vitamins, herbals, and supplement drugs were captured along with the dose and time since the patient's last dose. Drug histories were gathered in a structured format. Initially, we asked, "what medications have you taken in the last 48 hours?" We then asked specifically about the use of prescription drugs, nonprescription drugs, vitamins, herbals, or traditional drugs, and dietary supplements. All reported drugs were recorded. When available, pill bottles were obtained to verify drug doses. If the patient had difficulty recalling the prescription name, their pharmacy was contacted to ensure accuracy of the obtained history. Over-the-counter nonprescription combination formulations were reconciled using Internet pictures to verify the specific product ingested. The ED medical record was abstracted manually, and medications administered in the ED or prescribed at ED discharge were recorded. Patient demographic details were also abstracted from the ED medical record (Table 2).

2.3. Interaction identification

All patient-reported drugs were categorized as a CYP2C19 substrate, inhibitor, inducer, or not CYP2C19 dependent using the University of Indiana CYP450 Interaction Table [30]. The presence of CYP2C19 interaction was considered dichotomous; interaction was present if the subject had taken a home CYP2C19-dependent drug and was administered or prescribed a CYP2C19-dependent drug in the ED. We considered clinically significant drug-drug interactions to include drugs with narrow therapeutic windows. Those drugs included warfarin, clopidogrel, carbamazepine, oxcarbazepine, and topiramate.

2.4. Genotyping

Fifty-three patients were randomized for CYP2C19 genotyping by a random number generator. Genotyping was provided by LabCorp using the CYP2D6/2C19 Amplichip. Genotyping with the Amplichip accounts for 3 distinct CYP2C19 polymorphisms categorizing the individual's genotype into 1 of 3 predicted metabolizer groups: poor metabolizer, intermediate metabolizer, or extensive metabolizer [31].

Table 2
Patient demographics

Demographic variable	Total cohort, N = 502	Genotyped cohort, n = 53
Age, y (range, IQR)	39 (18-89, 22-53.3)	51 (20-85, 33-63.5)
Male, n (%)	198 (39.4)	23 (43.4)
Ethnicity/race		
Hispanic/Latino, n (%)	98 (19.5)	17 (32.1)
White, n (%)	326 (64.9)	40 (75.5)
African American, n (%)	162 (32.3)	11 (20.8)
Asian, n (%)	9 (1.8)	0
American Indian/Alaskan Native, n (%)	19 (3.8)	2 (3.8%)
Native Hawaiian/Pacific Islander, n (%)	6 (1.2)	0
Median no. of drugs taken (range, IQR)	3 (0-33, 1-6)	5 (1-17, 3-11)