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Relationship Between Characteristics of Medications and Drug-Induced Liver Disease Phenotype and Outcome

Raj Vuppalanchi[1], **Raghavender Gotur**[1], **K. Rajender Reddy**[2], **Robert J. Fontana**[3], **Marwan Ghabril**[1], **Andrzej S. Kosinski**[4], **Jiezhun Gu**[4], **Jose Serrano**[5], and **Naga Chalasani**[1]

[1]Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA [2]Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania [3]Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan [4]Duke Clinical Research Institute, Durham, North Carolina [5]Liver Disease Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland

Abstract

Background & Aims: It is not known if specific characteristics of medication are associated with type of drug-induced liver injury (DILI) or outcome. We examined the relationships among select characteristics of medications and DILI phenotype and outcome.

Author for Correspondence Naga Chalasani, MD, FACG David W. Crabb Professor & Director Division of Gastroenterology and Hepatology Indiana University School of Medicine 1050 Wishard Boulevard, RG 4100 Indianapolis, IN 46202 Tel (317) 278-0414 Fax (317) 278-1949 nchalasa@iu.edu.

Author Contributions
Study concept and design: R.V., N.C., K.R.R.
Acquisition of data: R.G., R.V.
Analysis and interpretation of data: R.V., N.C.
Drafting the manuscript: R.V., N.C.
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Methods: We analyzed 383 cases of DILI caused by a single orally administered prescription agent from the DILI Network Prospective Study with causalities of definite, highly likely, or probable. Relationship of daily dosage (≥ 50 mg vs. ≤ 49 mg), preponderance of hepatic metabolism (≥50% vs <50%), or Biopharmaceutics Drug Disposition Classification System (BDDCS) class (1–4, based on solubility and metabolism of the drug) were compared with clinical characteristics and outcomes.

Results: Compared to cases of DILI in the <50 mg/day group, those associated with daily dosages ≥50 mg had shorter latency (median 38 days vs 56 days; *P*=.03) and a different biochemical pattern of liver injury (*P*=.04); no differences in pattern of injury, recovery, severity, or outcome were observed. Patients with DILI caused by medications with or without preponderant hepatic metabolism did not differ in clinical characteristics or outcomes. Compared to other classes of BDDCS, DILI caused by BDDCS class 1 medications had significantly longer latency (*P*<.001) and greater proportion of hepatocellular injury (*P*=.001). However, peak liver biochemical values and patients' time to recovery, disease severity, and outcomes did not differ among the 4 BDDCS classes.

Conclusions: Characteristics of medications (dosage, hepatic metabolism, and solubility) are associated with features of DILI such as latency and pattern of liver injury, but not with recovery, severity, or outcome.

Keywords

DILIN; liver toxicity; overdose; side effect; ALT

INTRODUCTION

Idiosyncratic drug-induced liver injury (DILI) likely occurs due to complex interplay among host factors, environmental variables and the nature of the offending agent.[1] Research efforts over the last decade have therefore focused primarily on the understanding of the genetic factors that increase an individual's susceptibility to DILI.[2, 3] However, medication characteristics such as daily dose administered and their metabolism profile are starting to emerge as potential risk factors for DILI.[4-7]

It was initially pointed out by J. Uetrecht that drugs given at a daily dose of 10 mg or less are rarely if ever associated with a high incidence of DILI and majority of the drugs that were either withdrawn from the market or received a black box warning due to hepatotoxicity were prescribed at daily doses greater than 50 mg.[8] Lammert et al. reported a statistically significant relationship between daily dose of oral medicines and reports of liver failure, liver transplantation and death due to DILI.[6] Lammert et al. also reported that compounds with >50% hepatic metabolism had significantly higher frequency of ALT >3X ULN, liver failure and fatal DILI.[4] Recently, Chen et al. suggested a combined effect of daily dosage of >100 mg and high lipophilicity on the risk of DILI among medications approved by the Food and Drug Administration. [5]

Drugs with higher lipophilicity resulting in increased permeability and uptake by hepatocytes may undergo greater biotransformation leading to toxic metabolites and

heightened susceptibility to DILI.[7, 9] Conversely, drugs with low lipophilicity have low permeability, undergo less hepatic metabolism and may be at lower risk for causing DILI as they are primarily eliminated unchanged into the urine and bile.[7, 9] However, some drugs (cefadroxil, cephradine, levofloxacin, loracerbef, ofloxacin, sotalol and pregabalin) classified as having low permeability exhibit high absorption ≥90% due to presence of intestinal drug transporters.[10] By evaluating metabolism, not permeability or lipophilicity, drugs can be categorized into four classes according to their solubility and metabolism using the Biopharmaceutics Drug Disposition Classification System (BDDCS) classification: **Class 1** (High solubility- Extensive metabolism), **Class 2** (Low solubility- Extensive metabolism), **Class 3** (High Solubility- Poor metabolism), and **Class 4** (Low solubility – Poor Metabolism).[11-13] The current study investigated the relationship between DILI phenotypic characteristics and select drug properties such as a) daily dosage: ≥50 mg b) predominant hepatic metabolism (>50%) and c) BDDCS classes 1-4.

METHODS

We extracted data from the U.S. DILIN prospective study database with the following eligibility criteria: (a) Cases that have been causality adjudicated with a DILIN causality score probable or higher as described previously[16, 17] and (b) DILI caused by single oral prescription agent taken daily. A DILIN severity score was assigned according to a previously published scale from 1 (mild with serum total bilirubin <2.5 mg/dL) to 5 (death or liver transplantation).[14, 15] Information regarding the drug dosage administered to the patient was extracted from the DILIN database (DILIMED). Drugs were categorized based on daily dosage into those with and without appreciable hepatic metabolism based on information within drug's approved package insert, DrugBank (www.drugbank.ca) or DailyMed (dailymed.nlm.nih.gov). BDDCS classification of the drugs was obtained from previously published literature.[11] By evaluating metabolism, not permeability, BDDCS is not subject to variability due to transporter effects.[11, 12] Demographic, biochemical and clinical outcomes were extracted and analyses were performed on the following variables (a) latency (time from drug exposure to DILI onset), (b) time to peak values for total bilirubin, (c) time to recovery (peak to 50% reduction in total bilirubin), (d) DILIN severity score, and (e) outcomes (hospitalization, liver related death and transplant).

The data analyses were performed at the Duke Clinical Research Institute, the data coordinating center of the DILIN. SAS v 9.2 was used to aid all analyses. Continuous variables were summarized with mean and standard deviation or median and interquartile range (IQR). Categorical data were expressed as counts and proportions. Fisher's exact test was used to analyze differences between groups for the categorical data and differences between groups for continuous variables were assessed with a non-parametric test (Wilcoxon test for two groups or Kruskal–Wallis one-way analysis of variance for more than two groups). P-values less than 0.05 were considered statistically significant. There was no adjustment made for multiplicity of comparisons. The authors had access to the study data and have reviewed and approved the final manuscript.

RESULTS

A total of 1083 DILI subjects enrolled up to March 2012 were screened to identify 383 cases that met the eligibility criteria (Fig 1). A total of 107 drugs were responsible for these DILI episodes. We could not obtain the details of hepatic metabolism on 3 (febuxostat, investigational drug, ranitidine) and the specifics of BDDCS in 8 drugs (benzonatate, deferasirox, flavocoxid, investigational drug, phentermine, regorafenib, salsalate, and thiamazole). The mean age of the patients in the study cohort was 50 ± 18 years with 63% women and 79% Caucasian.

Relationship between drug dose and DILI phenotype and outcomes

Episodes of DILI due to drugs with daily dosage ≥ 50 mg had significantly shorter latency period as compared to those who received ≤ 49 mg per day [38 (20-96) vs.56 (30-208) days, *P*=.03]. The pattern of liver injury (Cholestatic/Mixed/Hepatocellular) at onset was also significantly different between two dosage groups (*P*=.04), with a greater proportion of cholestatic liver injury in ≤ 49 mg per day. However, no other significant differences were noted between the groups with regard to peak values of liver biochemistries, time to peak, and time to recovery (Table 1). The DILIN severity scores were not significantly different based on dose classification (*P*=.3). Similarly, clinical outcomes such as hospitalization rate, liver-related death and liver transplantation rate were not different between two groups (Table 1).

Relationship between drug metabolism and DILI phenotype and outcomes

In the current cohort, a higher number of cases had DILI from drugs that underwent significant hepatic metabolism (n=305) compared to those without hepatic metabolism (n=71). The two groups otherwise did not differ with regard to variables such as latency, pattern of liver injury, time to peak, and time to recovery. The DILIN severity scores were not significantly different based on hepatic metabolism classification (*P*=.3). Outcomes such as hospitalization rate (55% vs. 44%, *P*=.3), liver-related death (2% vs. 5.6%, *P*=.7) and liver transplant (3.3% vs. 1.4%, *P*=.7) were not different between two groups (Table 1).

Relationship of BDDCS classification with DILI phenotype and outcomes

A total of 99 drugs belonging to BDDCS Classes 1 through 4 were responsible for these DILI episodes (Table 2). The distribution of cases belonging to each BDDCS group was different with underrepresentation of DILI cases caused by BDDCS Class 4 agents. Four compounds (ciprofloxacin, nitrofurantoin, cefdinir and levonorgestrel//ethinylestradiol) accounted for all cases of DILI belonging to BDDCS Class 4 (Table 2). DILI cases from drugs belonging to Class 4 differed from other groups in having a significantly lower percentage of jaundiced patients (*P*<0.001), absolute eosinophilia >500/uL (*P*=.008) with lower peak ALT (p=0.001) and AST (*P* <0.001).The groups differed significantly with regard to latency period with Class 1 having the longest latency period (*P* <0.001) (Table 1). The pattern of liver injury at onset was significantly different between the groups (*P* <0.001) with Class 1 having the highest proportion of HC pattern (76%). However, no significant differences were noted between the groups with regard to time to peak total bilirubin and time to recovery. Hospitalization rate was significantly different among the groups (*P*=.01)

with Class 4 having the lowest rates at 45% (Table 1). However, outcomes such as liver related death (*P*=.1) and transplantation rate (*P*=.3) were not different (Table 1).

DISCUSSION

Although prior studies have suggested a relationship between drug characteristics and their propensity to cause DILI, data regarding drug characteristics and DILI phenotype are lacking. In the current study, we leveraged the unique features of DILIN database to examine the relationships among drug characteristics and DILI phenotype and outcomes. The current observations of shorter latency with daily dosage of ≥ 50 mg and a higher peak ALT with drugs that undergo hepatic metabolism demonstrate the importance of the intrinsic drug properties as a potential factor for the development of a DILI event. These findings also suggest that a threshold level of parent drug, metabolite, and / or adducts is a prerequisite for the DILI event. However, lack of any significant differences in the clinical outcomes supports the current understanding that the mechanism of injury and subsequent recovery may be predominantly mediated by the host immune response or host susceptibility due to genetic or acquired inability to detoxify hepatotoxic drug intermediates.[1, 16, 17] Further studies are needed to examine how these properties influence mechanisms involved in DILI such as CYP bioactivation reactions, covalent binding, or mitochondrial toxicity.[18, 19]

Our examination of the relationship among drug properties such as aqueous solubility / gastrointestinal permeability using BDDCS classification[20, 21] and DILI phenotype or outcomes led to some novel observations. First, drugs belonging to Class 4 (cefdinir, ciprofloxacin, nitrofurantoin, and levonorgestrel with ethinylestradiol) were incriminated in lower percentage of DILI patients, possibly because BDDCS class 4 drugs are underrepresented in orally approved drugs. These BDDCS class 4 drugs were associated with a significantly lower peak serum aminotransferase levels presumably due to their low permeability and solubility resulting in reduced uptake and lower hepatic biotransformation. A detailed review of these cases showed instances where prolonged exposure of the drug occurred (in some cases of nitrofurantoin exposure occurred for several years) before the DILI episode occurred. Second, the current study identified 81% of the drugs causing DILI episodes as undergoing extensive hepatic metabolism, suggesting that a reactive metabolite intermediate, rather that the native drug may be responsible for the development of a DILI event, possibly through the formation of adduct complexes, acting as neoantigens.

Autoimmune DILI is often associated with presence of serum autoantibodies directed against hepatic cytochrome P450s or other hepatic proteins.[22] The covalent binding of the drug or reactive metabolite to liver microsomal proteins results in formation of a neoantigen with subsequent injury from immune response.[23, 24] It is thus plausible that drugs that belong to BDCSS class 1 and 2 (Extensive metabolism) may be at increased risk of causing autoimmune DILI. In the current study, we observed that several drugs that have previously been implicated to cause autoimmune DILI[22] belonged to BDCSS Class 1 (hydralazine, minocycline, propylthiouracil, methylphenidate and diclofenac) and 2 (atorvastatin, imatinib, fenofibrate and terbinafine) (Table 2). However, two drugs with definite association with autoimmune DILI i.e., methyldopa (BDCSS Class 3) and nitrofurantoin

(BDCSS Class 4) diverge from this pattern suggesting additional role of host related factors as being critical for a DILI event.

Lastly, the unique strengths of the DILIN cohort such as the ability to examine DILI cases with strong causality (1, 2, or 3) and availability of prospectively captured DILI phenotype and outcomes allowed us to perform the current study. The pitfalls common in the literature such as DILI case definition and causality adjudication are minimized in the DILIN prospective study because of its study design. [14, 15, 25] The current study failed to find any significant differences in clinic outcomes based on daily dosage in contrast to the earlier study by Lammert et al. who evaluated the Swedish registry. It is likely that these differences could be related to the DILIN registry prospective protocol and the current study design that included only DILI cases from single agent and with causality limited to the scores of 1, 2 or 3. It is also possible that lack of relationship between drug metabolism as well as of BDDCS classification with clinical outcomes might be due to lack of adequate sample size.

In summary, drug characteristics such as daily dosage ≥50 mg and BDDCS Class 1 are related to select aspects of DILI phenotype. However, the severity of liver disease and outcomes are not associated with drug characteristics. We speculate that DILI outcomes may be more related to host response rather than drug characteristics.

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Abbreviations

BDDCS:	Biopharmaceutics Drug Disposition Classification System
DILI:	Drug-Induced Liver Injury
DILIN:	Drug-Induced Liver Injury Network
ULN:	Upper Limit of Normal

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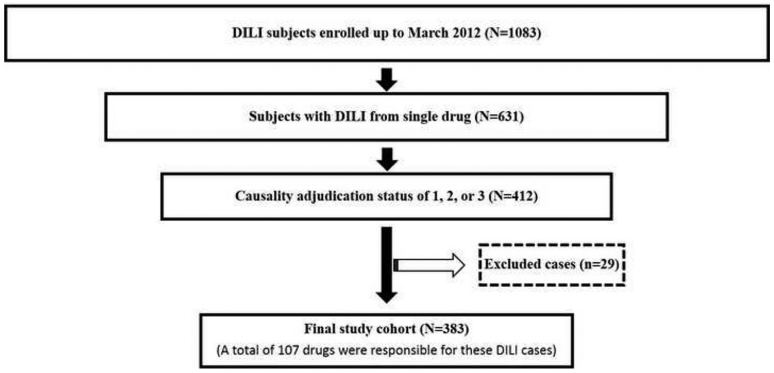

Figure 1.

Flowchart describing the selection of the study population. A total of 1083 subjects with drug induced liver injury (DILI) were enrolled up to March 2012. Among these, 631 subjects had DILI from a single drug. After causality adjudication, there were 412 subjects with adjudication status of definite, highly likely, and probable (1, 2 or 3). An additional 29 cases were excluded due to unknown dosage, drug start/stop date or mode of administration. The final study cohort consisted of 383 DILI cases resulting from 107 different drugs satisfied the study inclusion criteria: (a) DILI occurring from a single agent, (b) administered orally, (c) known daily dosage, and (d) causality of 1, 2 or 3.

Table 1

Relationship between drug characteristics and the DILI phenotype and outcomes (N=383).

	Latency (days)	Pattern of liver injury at onset (C/M/HC, %)	Time to Peak (days)	Time to Recovery (days)	Hospitalization (%)	Liver related Death (%)	Transplant (%)
Daily dose							
≥ 50 mg (n =324)	38 (20-96)	21/25/54	8 (2-15)	31 (13-51)	52	2.8	3.4
≤49 mg (n=53)	56 (30-208)	32/11/57	10 (4-22)	36 (12-70)	62	1.9	0
	(p=0.03)	(p=0.040)	(p=0.1)	(p=0.3)	(p=0.2)	(p=1.0)	(p=0.4)
Hepatic Metabolism							
Yes (n=305)	42 (25-100)	23/24/53	8 (2-16)	33 (13-56)	55	2.0	3.3
No (n=71)	34 (16-101)	23/21/56	7 (2-17)	31 (12-45)	47	5.6	1.4
	(p=0.3)	(p=0.9)	(p=0.9)	(p=0.3)	(p=0.2)	(p=0.1)	(p=0.7)
Biopharmaceutics Drug Disposition Class							
Class 1 (n=118)	81 (43-214)	12/12/76	7 (2-14)	27 (12-44)	53	2.5	5.1
Class 2 (n=96)	35 (43-214)	25/29/46	10 (3-23)	31 (10-55)	68	2.1	1.0
Class 3 (n=112)	28 (16-44)	32/29/39	7 (1-13)	38 (17-53)	46	0.9	1.8
Class 4 (n=38)	38 (15-568)	26/24/50	11 (3-22)	25 (7-49)	45	7.9	2.6
	(p<0.001)	(p<0.001)	(p=0.1)	(p=0.1)	(p=0.01)	(p=0.1)	(p=0.3)

All values are expressed as median (IQR) unless otherwise expressed. R ratio was calculated by dividing the ALT by the ALP from initial blood test, using multiples of the ULN for both values. R ≤ 2 Cholestatic (C) pattern of DILI, 2 < R < 5 Mixed (M) pattern of DILI, or R > 5: Hepatocellular (HC) pattern of DILI.

Table 2

List of drugs implicated in the DILI episode. Drugs arranged as per Biopharmaceutics Drug Disposition Classification System (BDDCS) class. A total of 99 drugs with BDDCS class of 1, 2, 3 or 4 were responsible for 372 cases of DILI. Drugs that are underlined have been associated with autoimmune DILI phenotype.

Class 1 (High solubility – Extensive metabolism) (n=118)	Class 2 (Low solubility – Extensive metabolism) (n=99)	Class 3 (High solubility – Poor metabolism) (n=115)	Class 4 (Low solubility – Poor metabolism) (n=40)
ALFUZOSIN (n=1)	ACITRETIN (n=3)	AMOXICILLIN (n=6)	CEFDINIR (n=1)
ALISKIREN (n=1)	ALLOPURINOL (n=2)	AMOXICILLIN	CIPROFLOXACIN (n=11)
ATOMOXETINE (n=3)	AMIODARONE (n=4)	W/CLAVULANIC ACID	LEVONORGESTREL
AZATHIOPRINE (n=4)	ATORVASTATIN (n=4)	(n=61)	W/ETHINYLESTRADIOL
BUPROPION (n=3)	BOSENTAN (n=1)	ATENOLOL (n=1)	(n=1)
CLINDAMYCIN (n=1)	CARBAMAZEPINE (n=2)	AZITHROMYCIN (n=4)	NITROFURANTOIN
CYCLOPHOSPHAMIDE (n=2)	CELECOXIB (n=2)	BENAZEPRIL W/HCTZ	(n=27)
DANTROLENE (n=1)	DISULFIRAM (n=2)	(n=1)	
DICLOFENAC (n=9)	DRONEDARONE (n=2)	CEFACLOR (n=1)	
DULOXETINE (n=6)	DROSPIRENONE	CEFADROXIL (n=1)	
ESCITALOPRAM (n=1)	W/ETHINYLESTRADIOL (n=1)	CEFALEXIN(n=1)	
ESTRADIOL (n=1)	ETODOLAC (n=2)	CEFUROXIME (n=1)	
ETHOSUXIMIDE (n=1)	EZETIMIBE W/SIMVASTATIN	DOXYCYCLINE (n=4)	
FLUOXETINE (n=1)	(n=2)	ERYTHROMYCIN (n=2)	
FLUVASTATIN (n=1)	FEBUXOSTAT (n=1)	FLUCONAZOLE (n=2)	
HYDRALAZINE (n=4)	FENOFIBRATE (n=2)	GABAPENTIN (n=1)	
ISONIAZID (n=32)	IMATINIB (n=3)	LEVOFLOXACIN (n=4)	
LABETALOL (n=1)	ITRACONAZOLE (n=1)	LISINOPRIL (n=2)	
LETROZOLE (n=1)	LAMOTRIGINE (n=5)	METHOTREXATE (n=1)	
METHYLPHENIDATE (n=1)	LANSOPRAZOLE (n=1)	METHYLDOPA (n=8)	
MINOCYCLINE (n=22)	LAPATINIB (n=1)	METOCLOPRAMIDE	
NICOTINIC ACID (n=2)	LEFLUNOMIDE (n=2)	(n=1)	
PROMETHAZINE (n=1)	MELOXICAM (n=2)	MOXIFLOXACIN (n=2)	
PROPYLTHIOURACIL (n=2)	MERCAPTOPURINE (n=5)	PENICILLAMINE (n=1)	
PYRAZINAMIDE (n=1)	MESALAZINE (n=1)	PRAVASTATIN (n=1)	
QUETIAPINE (n=1)	METAXALONE (n=1)	RANITIDINE (n=2)	
SERTRALINE (n=1)	MONTELUKAST (n=2)	ROSUVASTATIN (n=4)	
TAMOXIFEN (n=4)	NEVIRAPINE (n=2)	TOPIRAMATE (n=3)	
VALACICLOVIR (n=1)	OLANZAPINE (n=1)		
VALPROIC ACID (n=5)	OXAPROZIN (n=1)		
VERAPAMIL (n=3)	PHENYTOIN (n=8)		
	PRASUGREL (n=1)		
	QUINAPRIL (n=1)		
	SIMVASTATIN (n=4)		
	SULFASALAZINE (n=1)		

Class 1 (High solubility – Extensive metabolism) (n=118)	Class 2 (Low solubility – Extensive metabolism) (n=99)	Class 3 (High solubility – Poor metabolism) (n=115)	Class 4 (Low solubility – Poor metabolism) (n=40)
	SULFAMETHOXAZOLE W/TRIMETHOPRIM (n=12)		
	TACROLIMUS (n=1)		
	TELITHROMYCIN (n=5)		
	TEMOZOLOMIDE (n=1)		
	TERBINAFINE (n=5)		
	THALIDOMIDE (n=1)		
	VORICONAZOLE (n=1)		

Solubility refers to solubility in water: High solubility compound at the highest marketed dose strength would be soluble in 250 mL of water over the pH range of 1–7.5 at 37°C.