Relationship Between Daily Dose of Oral Medications and Idiosyncratic Drug-Induced Liver Injury: Search for Signals

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Idiosyncratic drug-induced liver injury (DILI) is traditionally thought not to be dose-related. However, it has been pointed out that most medicines that were withdrawn from marketing or received a black-box warning because of hepatotoxicity were prescribed at daily doses greater than 50 mg/day. To examine the relationship between daily dose of medications and idiosyncratic DILI, we conducted a study with two aims. First, using two pharmaceutical databases, we examined the relationship between daily dose of commonly prescribed medicines in the United States and reported frequency of their selected hepatic adverse events. Second, we examined serious DILI cases reported to the Swedish Adverse Drug Reactions Advisory Committee (1970-2004) for any signals supporting the relationship between daily dose and idiosyncratic DILI. Medications were categorized into ≤10 mg/day, 11-49 mg/day, and ≥50 mg/day groups. Among US prescription medicines, a statistically significant relationship was observed between daily dose of oral medicines and reports of liver failure ($P = 0.009$), liver transplantation ($P < 0.001$), and death caused by DILI ($P = 0.004$) but not alanine aminotransferase (ALT) > 3 × upper limit of normal ($P = 0.10$) or jaundice ($P = 0.16$). Of 598 eligible Swedish DILI cases, 9% belonged to the ≤10 mg/day group, 14.2% to the 11-49 mg/day group, and 77% of cases were caused by medications given at dose ≥50 mg/day. A statistically significant relationship was noted between daily dose and poor outcome (death or liver transplantation) of Swedish DILI cases (2%, 9.4%, and 13.2% in ≤10, 11-49, and ≥50 mg/day groups, respectively, $P = 0.03$). *Conclusion:* These data suggest a relationship between daily doses of oral prescription medications and idiosyncratic DILI. More studies are needed to validate these observations and to explore their implications. (HEPATOLOGY 2008;47:2003-2009.)

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Idiosyncratic drug-induced liver injury (DILI) is rare, but when it occurs it may have serious consequences.[1] It is one of the most frequent causes of acute liver failure in the United States[1,2] and in fact is one of the most common reasons for not receiving approval or for withdrawal from marketing by the United States Food and Drug Administration.[3] The pathogenesis of idiosyncratic DILI is not well understood but is generally thought to be unpredictable and not dose-dependent. However, it has been pointed out that most drugs that either have been withdrawn from the market or have received a black box warning due to hepatotoxicity were prescribed at daily doses greater than 50 mg, suggesting some dose relationship[4] (Table 1). There is some relationship between daily dose of a medication (for example, statins, bosentan) and the reported frequency of elevated aminotransferases, suggesting that in some instances DILI may be dose-dependent.[5,6] Anecdotally, we have observed many instances in which individuals developed clear-cut hepatotoxicity on

Abbreviations: ALT, alanine aminotransferase; APAP, acetaminophen; DILI, drug-induced liver injury.

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Table 1. Daily Doses of Medications That Either Have Been Withdrawn from the United States Market or Have Received Hepatotoxicity Warning by the FDA

Withdrawn from Marketing		
Compound	**Year**	**Daily Dosage**
Iproniazid	1956	100–250 mg
Ticrynafen	1979	250–500 mg
Benoxaprofen	1982	600 mg
Bromlenac	1998	75–100 mg
Troglitazone	2000	400–600 mg
Ximelagalran*	2006	48–72 mg

Hepatotoxicity Warnings			
Strong Warning of Serious Hepatotoxicity		**Moderate Warning of Serious Hepatotoxicity**	
Compound	**Daily Dosage**	**Compound**	**Daily Dosage**
Valproic acid	250–1250 mg	Zileuton	1600–2400 mg
Ketoconazole	200–800 mg	Tacrine	40–160 mg
Nicotinic acid	100–4500 mg	Labetalol	200–400 mg
Rifampin	300–1200 mg	Diclofenac	75–200 mg
Chlorzoxazone	750–3000 mg	Dantrolene	25–400 mg
Isoniazid	300 mg		
Dantrolene	25–400 mg		
Nefazadone	200–600 mg		
Telethromycin	800 mg		
Nevirapine	200–400 mg		
Atomoxetine	40–100 mg		
Infliximab	5 mg/kg		

Assigned as Second-line Agents Because of Hepatotoxicity	
Compound	**Daily Dosage**
Pemoline	mean 56-75 mg, max 112.5 mg
Tolcapone	300 mg
Trovafloxacin	50–200 mg
Febamate	1200–3600 mg

NOTE. It is striking that almost all these compounds were given at doses greater than 50 mg per day.

*Was not approved by FDA for marketing in the USA and was withdrawn from worldwide marketing.

ceived at stable doses for a lengthy period. For example, a middle-aged woman without known underlying liver disease or alcoholism developed pronounced hepatotoxicity caused by duloxetine very soon after increasing its dose to 60 mg/day, although she received 30 mg/day duloxetine for many weeks with no complications (unpublished data). These observations raise the possibility that some relationship may exist between daily dose of a medication and its propensity to exhibit hepatotoxicity. However, this has not been previously studied in a formal fashion.

To explore for an association between daily dose of medications and idiosyncratic DILI, we conducted a study with two specific aims. First, using two comprehensive pharmaceutical databases, we examined the relationship between daily dose of oral medications that are commonly prescribed in the United States and reported amined the daily doses of oral medications that have been implicated in the reports of suspected hepatic adverse drug reactions submitted to the Swedish Adverse Drug Reactions Advisory Committee during the period 1970 to 2004.

Materials and Methods

First Aim. We used a publicly available pharmacy database (www.drugtopics.com) to extract the names of the top 200 brand and top 200 generic medications by prescription volume in the United States during the year 2005.[7,8] Duplicate compounds were reduced to a single entry, and nonoral medications were removed. List compilation yielded 230 medications available for further consideration. These compounds were further categorized into dosage groups of 10 mg or less, 11 to 49 mg, and 50 mg or greater based on daily recommended doses (Table 2). The compounds with broad ranges of recommended daily dose were placed within dosage groups based on the average of maximum and minimum recommended daily dose. For example, atorvastatin, with a daily recommended dose ranging between 10 and 80 mg (average, 45 mg) was placed in the 10-mg to 50-mg group. We subsequently reviewed each of these medications to assess whether they were ever reported to have caused selected hepatic adverse events, using the Thompson's Micromedex Drugdex System. Drugdex is one of the most comprehensive pharmacy databases, consisting of package insert data and published literature.[9] Hepatic adverse events selected for this specific aim were alanine aminotransferase (ALT) greater than 3 times the upper limit of normal, cholestatic jaundice, liver failure, liver transplantation, and death caused by hepatic injury. To ensure completeness, each listed compound was cross-checked in the PubMed, Adverse Event Reporting System database, and the *Physicians' Desk Reference*.[10-12] For each listed compound, we extracted whether these selected hepatic adverse events were reported rather than the number of events reported.

Second Aim. All reports of suspected drug-induced liver injury received by the Swedish Adverse Drug Advisory Committee since 1970 have been computerized. The reporting of fatal, otherwise serious, and new reactions has been compulsory since 1975. In a previous paper, the number and nature of suspected adverse drug-induced liver disease associated with fatalities or leading to liver transplantation between 1966 and 2002 were reported (Swedish DILI death/transplant cases).[13] In a subsequent paper, all cases of suspected DILI with concomitant jaundice reported between 1970 and 2004 were reviewed for

Table 2. Most Commonly Prescribed Medicines in the United States Categorized into Three Dose Groups

≤10 mg/day (n = 54)	11–49 mg/day (n = 83)	≥50 mg/day (n = 93)
Actonel	Ahilify	Acyclovir
Alprazolain	Accupril	Allegra-D 12 hour
Altace	Aciphex	Allopurinol
Amaryl	Actos	Amiodarone
Aricept	Adderall XR	Amitriptyline
Arimidex	Ambien	Amoxicillin
Avandia	Atacand	Amoxicillin/clavulanate
Benazepril	Baclofen	Aspirin, Enteric-Coat
Benztropine	Benicar	Atenolol
Bisoprolol/HCTZ	Benicar HCT	Atenolol chlorthal
Bumetanide	Bextra	Atomoxctine hyrdochloride
Beoestin	Buspirone HCl	Azithromycin
Cialis	Captopril	Benzonatate
Clannex	Citalopram HBR	Bupropion hydrochloride
Clonazepam	Clorazepate dipot	Carhamazepine
Colchicine	Concerta	Carbidopa/levodopa
Coumadin	Coreg	Carisoprodol
Detrol LA	Cozaar	Cefdinir
Diazepam	Crestor	cefprozil
Digitek	Cymbalta	Celuroxime Axctil
Ditropan	Diovan	Celecoxib
Doxazosin	Diphenhydramine tabs	Cephalexin
EE/ethynodiol di	Diphenoxylate w/Atro	Cimetidine
Felodipine ER	Doxepin	Ciprofloxacin HCl
Flomax	Effexor XR	Clarithromycin
Fosinopril sod	Farnotidine	Clopidrogel hydrogen sulfate
Glipizide XL	Flexeril	Diclofenac Sodium
Glyburide	Fluoxetine	Diclofenac sodium/misoprostol
Hyoscyamine	Fosamax	Dicyclomine HCl
Indapamide	Furoscmide oral	Diltiazem hydrochloride
Levonorgestrel	Geodon oral	Docusate sodium
Lorazepam	Hydralazine	Doxycycline
Lotrel	Hydrochlorothiazide	Etodolac
Lowogestrel	Hydroxyzine	Fenofibrate
Lunesta	Imitrex Oral	Fexofenadine hydrochloride
Mavik	Indomethacin	Fluconazole
Metolazone	Isosorbide mononitrate	Gabapentin
Mirapex	Lescol	Gemfibrozil
Mobic	Levitra	Glyburide/metformin HCl
Namenda	Lexapro	Hydrochlorothiazide/valsartan
Norethindrone/ee	Lipitor	Hydrocholorthiazide/irbesartan
Norgestimate/ee	Lisinopril	Hydroxychloroquine
Norvasc	Lisinopril/HCTZ	Hydroxyzine Pamoate
Prednisone oral	Lovastatin	Ibuprofen
Premarin	Meclizine HCl	Imipramine HCl
Prempro	Methadose	Irbesartan
Proscar	methlyprednis	Labetalol
Risperdal	Metoclopramide	Lamotrigine
Synthroid	Metoprolol tartrate	Levetiracetam
Temazepam	Micardis	Levofloxacin
Terazosin	Mirtazapine	Lithium Carbonate
		Losartan potassium-hydrochlorothiazide
Tizanidine HCl	Nadolol	Mesalamine
Yasmin 28	Nexium	Metaxalone
Zyrtec	Nifedipine ER	Metformin
	Omeprazole	Metformin/rosiglitazone
	Oxycodone	Methocarbamol
	Oxycontin	Metronidazole Tabs
	Paxil CR	Minocycline
	Phentermine	Modafinil
	Piroxicam	Moxifloxacin hydrochloride
	Pravachol	Mytussin AC
	prednisolone	
	Prevacid	Nabumetone
	Prochlorperaz mal	Naproxen
	Promethazine tabs	niacin
	Protonix	Nurtriptyline
	Relpax	Nitrofurantoin
	Ritalin-LA	Oseltamivir phosphate
	Singulair	oxcarbazepine
	Spironolactone	Penicillin VK
	Tamoxifen	Pentoxifylline
	Thyroid, Armour	Phenazopyridine HCl
	Timolol Maleate GFS	Phenobarbital
	Tuprol XL	Phenytoin
	Tramadol	Progesterone
	Triamterene w/HCTZ	Propranolol hydrochloride
	Tussionex	Quetiapine furnarate
	Viagra	Quinine sulfate
	Vytorin	Raloxifene hydrochloride
	Zelnorm	Ranitidine hydrochloride
	Zetia	Scrtraline
	Zocor	Sotalol
	Zyprexa	Telithromycin
		Terbinafine hydrochloride
		Tetracycline
		Theophylline SR
		Topiramate
		Trandolapril/verapamil
		Trazodone HCl
		Trimethoprim/Sulfa
		Valacyclovir hydrochloride
		Valproic Acid (divalproex sodium)
		Verapamil SR

(Swedish DILI jaundice cases).[14] Cases contained within these two data sets were retrieved, and duplicate entries were excluded from further consideration. The causality was rigorously assessed according to the International Consensus Criteria,[15-17] and all cases had least "possible" causality relationship. Apart from the daily dose of the implicated medication, the following information was retrieved from the reports: drug(s) suspected, results of peak aspartate aminotransferase, ALT, alkaline phosphatase, and bilirubin values, and outcome (recovery, death, or liver transplantation). Cases with more than one drug suspected to have caused DILI and acetaminophen alone or in combination with other drugs were excluded. Only oral medications were included in the analysis. The implicated medications were categorized into 10 mg or less, 11 to 49 mg, and 50 mg or greater based on the daily dosage. The objectives were to examine how many Swedish DILI cases belonged to each of these dosage groups and to explore the relationship between daily dose and outcome of Swedish DILI cases.

For aim 2, as a supplement to the Swedish DILI data,

Table 3. Association Between Daily Doses of Oral Prescription Medications and Hepatic Adverse Events

Number of Compounds Reported To Have Caused	≤10 mg (n = 54)	10–50 mg (n = 83)	≥50 mg (n = 93)	*P*-Value
ALT > 3 × ULN (n, %)	10 (19)	22 (27)	29 (31)	0.10
Jaundice (n, %)	18 (33)	33 (40)	42 (45)	0.16
Liver Failure (n, %)	9 (17)	10 (12)	30 (32)	0.009
Death (n, %)	6 (11)	9 (11)	26 (28)	0.004
Transplant (n, %)	0 (0)	2 (2)	12 (13)	<0.001
Prescriptions (median in 2005)	4,746,500	4,938,000	3,733,000	0.3

For example, 19% of compounds belonging to the <10 mg group have been reported to cause ALT > 3 ULN, whereas 27% of compounds belonging to the 10–50 mg group and 31% of compounds belonging to the >50 mg group (*P*-value = 0.10). Another example: 32% of compounds belonging to the >50 mg group have been reported to cause liver failure in comparison with 17% in the <10 mg group and 12% in the 10–50 mg groups ($P < 0.01$).

consisted of 270 DILI cases that required liver transplantation in the United States between 1990 and 2002.[18] Of these 270 cases, 133 were acetaminophen (APAP) related, and 137 were non–APAP related. We examined how many of these non-APAP cases belonged to 10 mg/day or less, 11 to 49 mg/day, and 50 mg/day or greater groups.

Statistics. For aim 1, proportions were used to describe the clinical dichotomous outcomes. The Kruskal-Wallis test compared the distribution of the number of times a compound was prescribed in 2005 among the three groups of compounds. The Cochran-Armitage trend test was applied for association between clinical outcomes and compounds. The overall logistic regression model linked the odds of ever reporting an incidence of clinical outcome to the covariate, three groups of compounds. For the validity of the model fitting for the transplant outcome, we used two groups of compounds, less than 50 mg versus 50 mg or greater, because none of the compounds in the less than 10 mg group had undergone transplantation. Estimated odds ratios and 95% confidence intervals were reported. For aim 2, descriptive statistics and Fisher's exact test were used to analyze the data. A *P* value of less than 5% was considered statistically significant. SAS (version 9.1, Cary, NC) was used for statistical analyses.

Results

Aim 1. There were 54 compounds in the 10 mg/day or less group, 83 in the 11-mg to 49-mg/day group, and 93 in the 50 mg/day or greater group (Table 2). In 2005, the total number of prescriptions written ranged from 1,258,000 to 34,230,000 for the 10 mg/day or less group, 1,260,000 to 47,829,000 for the 11-mg to 49-mg/day group, and 1,286,000 to 101,639,000 for the 50 mg/day or greater group. There was no statistically significant difference in the median number of prescriptions written in 2005 among these three groups ($P = 0.37$; Table 3).

There was a statistically significant relationship between daily dose and different hepatic adverse event, liver transplantation, or liver-related death (Tables 3 and 4). Seventeen percent of compounds belonging to the 10 mg/day or less group had been reported to cause liver failure, in comparison with 12% in the 11-mg to 49-mg/day group and 32% in the 50 mg/day or greater group ($P = 0.009$). No compounds belonging to the 10 mg/day or less group caused liver transplantation, in comparison with 2% in the 11-mg to 49-mg/day group and 14% in the 50 mg/day or greater group ($P < 0.001$). Eleven percent of compounds belonging to the 10 mg/day or less group and the 11-mg to 49-mg/day group were reported to have caused DILI-related deaths, in comparison with 28% of compounds belonging to the 50 mg/day or greater group ($P = 0.007$). There was no statistically significant

Table 4. Relationship Between Daily Dose and Different Hepatic Events: Results from the Logistic Regression Analysis

Outcome and Covariate	Odds Ratio	95% Confidence Interval	*P*-Value
ALT > 3 × ULN			
Compound			
≤ 10 mg	1.00		
11–490 mg	1.59	0.68–3.68	0.28
≥50 mg	1.99	0.88–4.50	0.10
Jaundice			
Compound			
≤10 mg	1.00		
11–49 mg	1.32	0.65–2.70	0.45
≥50 mg	1.65	0.82–3.31	0.16
Liver failure			
Compound			
≤10 mg	1.00		
11–49 mg	0.69	0.26–1.81	0.446
≥50 mg	2.38	1.03–5.50	0.042
Death			
Compound			
≤10 mg	1.00		
11–49 mg	0.97	0.33–2.91	0.961
≥50 mg	3.10	1.19–8.12	0.021
Transplant			
Compound			
<50 mg	1.00		
[illegible]	[illegible]	[illegible]	[illegible]

Table 5. Types of Liver Injury and Outcome Stratified According to Daily Dose: The Swedish Hepatic ADR Data (Total Eligible Cases = 598)

	≤10 mg/day	11–49 mg/day	≥50 mg/day
Number of DILI cases	53 (8.9%)	85 (14.2%)	460 (76.9%)
Pattern of injury			
Hepatocellular	34 (64.2%)	43 (50.6%)	231 (50.2%)
Cholestatic	13 (24.5%)	22 (25.9%)	124 (26.9%)
Mixed	6 (11.3%)	20 (37.8%)	104 (22.6%)
Outcome			
Death/liver transplantation*	1 (2%)	8 (9.4%)	61 (13.2%)*
Survived	52 (98%)	77 (90.6%)	399 (86.8%)
Top 200 prescribed medicines in Sweden in 2005			
Proportion belonging to each dose group	22.5%	27.5%	37.5%
Median # of prescriptions	249,197	360,149	215,760

*The proportion of patients who died/transplanted due to DILI was significantly higher in the ≥50 mg daily dose in comparison with the 11–49 mg/day and the ≤10 mg/day groups (13.2% versus 9.4% versus 2%. $P = 0.03$).

association between daily recommended dose of oral prescription medications and reports of ALT more than 3× the upper limit of normal or jaundice (Tables 3 and 4).

The logistic regression analyses showed that a significantly higher proportion of medications belonging to the 50 mg/day or greater group had liver failure (odds ratio, 2.38; 95% confidence interval, 1.03-5.50), liver transplantation (odds ratio, 10.00; 95% confidence interval, 2.18-45.81), or liver-related death (odds ratio, 3.10; 95% confidence interval, 1.19-8.12), whereas medications belonging to the 10 mg/day or less and 11-mg to 49-mg/day groups had no differences (Table 4).

Aim 2. After applying exclusion criteria to Swedish DILI death/transplant and jaundice cases, a total of 598 cases were eligible for further analyses (58% females, median age of 59 years (interquartile range, 42-74); 51% had hepatocellular type and 49% had cholestatic/mixed type of liver injury. Seventy-seven percent of Swedish DILI cases belonged to the 50 mg/day or greater group, whereas only 9% belonged to the 10 mg/day or less group, and 14% belonged to the 11-mg to 49-mg/day group (Table 5). The pattern of liver injury and patient outcomes in different dose categories are shown in Table 5. Only one patient treated with 10 mg/day or less died, and only very few other patients with a lower daily dose than 50 mg/day either died or underwent liver transplantation (Table 5). A statistically significant relationship was noted between daily dose and poor outcome (death or liver transplantation) of Swedish DILI cases (13.2%, 9.4%, and 2% in ≥50, 11-49, and ≤10 mg/day groups, respectively; $P = 0.03$). Selected details of patients belonging to the 10 mg/day or less group and the 11-mg to 49-mg/day group who had poor outcome after DILI event are shown in Table 6. As a control measure, we assessed the proportion of prescription medications and their prescription volume in Sweden that belong to each of these dosage groups. After excluding nonoral formulations from 200 most prescribed medicines in Sweden in 2005, 37.5% belonged to the 50 mg/day or greater group, 27.5% belonged to the 11-mg to 49-mg/day group, and 22.5% belonged to the 10 mg/day or less group. The median number of prescriptions written in 2005 in Sweden were 249,197 (range, 101,094-1,847,843) for the 10 mg/day or less group, 360,149 (range, 99,986-2,647,547) for the 11-mg to 49-mg/day group, and 215,760 (range, 104,073-3,601,864) for the 50 mg/day or greater group.

Of 137 non-APAP DILI cases that required liver transplantation in the United States between 1990 and 2002, after excluding cases caused by inhalation agents (n = 4), intravenous agents (n = 3), herbal agents (n = 7), amanita mushrooms (n = 9), and combination of agents (n = 3), 111 cases were further analyzed. Of these 111 cases, two cases were caused by compounds belonging to the 10 mg/day or less group, eight belonged to the 11-mg to 49-mg/day group, and 101 cases were reportedly caused by compounds with a daily recommended dose of 50 mg or greater (Table 7).

Table 6. Selected Details of Patients with Poor Outcome DILI (Death or Transplantation) Caused by Compounds Given at <50 mg Daily Dose: The Swedish Hepatic ADR Dataset

Sex/Age (yrs)	Medication	Daily Dose (mg/day)	Duration of Exposure (days)	Type	Outcome
Male/79	Donepezil	5	501	HC	Death
Male/64	Enalapril	10	60	Mixed	LT
Female/73	Omeprazole	40	300	HC	Death
Male/63	Simvastatin	20	90	HC	LT
Male/64	Rofecoxib	25	23	HC	LT
Female/74	Enalapril	30	60	HC	Death
Male/78	Simvastatin	20	90	HC	Death
Female/55	Hydralazine	25	180	HC	Death
Female/73	Dikumarol	40	120	CS	Death

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