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Interplay of gender, age and drug properties on reporting frequency of drug-induced liver injury

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ABSTRACT

We examined the effect of gender, age, and drug properties on liver events reporting frequency (RF) to assess patient- and drug-related risks for drug-induced liver injury (DILI). We performed a data-mining analysis of the WHO VigiBase™ to 1) identify drugs with gender- and age-biased RF and 2) characterize drug properties using the Liver Toxicity Knowledge Base. Age-, gender-specific Empirical Bayes Geometric Mean of relative reporting ratio of liver events with 90% confidence interval (CI) was calculated for 375 drugs with DILI potential. Forty-one drugs showed an increased RF in women, which had a higher prevalence of reactive metabolite formation and mitochondrial dysfunction and transporter inhibition. Fifty-nine drugs showed an increased RF in younger women (< 50 yrs), many of which had a signature pattern of hepatocellular injury. In contrast, half of 17 drugs that showed an increased RF in men had a cholestatic pattern. In the older group (≥ 50 yrs), 17 drugs showed an increased RF and had higher transporter inhibition, Cmax, and plasma protein binding, yet shorter plasma elimination. Specific drug properties were associated with gender- and age-biased liver events RF, suggesting possible interactions of drug properties, gender, and age in DILI development.

1. Introduction

Drug-induced liver injury (DILI) is one of the most common drug adverse reactions and a major reason for early termination of drug development and market withdrawal. In the general population, the incidence of DILI is 14–19 per 100,000 and increases to approximately 34 per 100,000 in healthcare settings (Bjornsson et al., 2013; Sgro et al., 2002; Shin et al., 2013). With drug cessation, most DILI is self-limited. Yet, DILI can result in urgent liver transplantation and death and remains one of the predominant causes of acute liver failure (Ostapowicz et al., 2002; Reuben et al., 2010; Russo et al., 2004). Previous population-based DILI studies reported that most (56%) DILI is symptomatic, with 12–22% requiring hospitalization; DILI registry studies reported that 8–20% progresses to chronic liver injury and 9–12% of patients with hepatocellular jaundice suffer death or liver transplantation (Andrade et al., 2005; Bjornsson et al., 2013; Fontana et al., 2014; Medina-Caliz et al., 2016; Sgro et al., 2002). Thus, DILI remains a serious clinical concern.

Despite recent advances, mechanisms involved in developing DILI and clinical factors influencing DILI risk are not fully understood. DILI is likely influenced by the interaction of drug properties and patient-specific factors (Chen et al., 2015). Drug properties associated with hepatotoxicity include: extensive hepatic metabolism, reactive metabolite formation, daily dose ≥ 100 mg, high lipophilicity, mitochondrial toxicity, and transporter inhibition (Boelsterli and Lim, 2007; Chen et al., 2013a; de Lima Toccafondo Vieira and Tagliati, 2014; Knowles et al., 2000; Lammert et al., 2008, 2010; Pauli-Magnus and Meier, 2006). Host genetic variants of HLA markers, drug-metabolizing enzymes, mitochondrial functions, transporter functions, cytokines and oxidative stress have been associated with DILI (Russmann et al., 2010). DILI clinical phenotype, histology, and outcomes appear to be influenced by age, gender and reproductive state (Lucena et al., 2009;

Abbreviations: DILI, drug-induced liver injury; DILIN, drug-induced liver injury network; HC, hepatocellular; CS/MIX, cholestatic/mixed; ALT, alanine aminotransferase; ALP, alkaline phosphatase; ULN, upper limit normal; ANA, antinuclear antibody; OR, odds ratio; CI, confidence interval; RF, reporting frequency; WHO, World Health Organization; LTKB, Liver Toxicity Knowledge Base; Cmax, maximum/peak drug concentration; T1/2, half life; MRP 2,3,4, multidrug resistance associated protein 2, 3 4; MedDRA, Medical Dictionary for Regulatory Activity; RRR, relative reporting ratio; EBGM, Empirical Bayes Geometric Mean of relative reporting ratio of liver events; FDA, food and drug administration; BDDCS, Biopharmaceutics Drug Disposition Classification System; ATP, Adenosine triphosphate; CYP, cytochrome

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Suzuki et al., 2017). Case series studies from DILI registries showed an overrepresentation of specific gender or age groups among DILI cases caused by specific drugs, which may imply potential drug-specific gender- or age-specific biases (deLemos et al., 2016; Fontana et al., 2013; Urban et al., 2017). However, due to a lack of controls, the interaction of age, gender and specific drug properties with DILI susceptibility remains uncertain.

In this study, we explored the potential interaction of drug properties and host factors and their association with the increased reporting frequency of liver events reported in a large adverse event reporting system. We performed a data-mining analysis using the World Health Organization (WHO) VigiBase™ and characterized drugs that demonstrated age-, gender-biased reporting frequency for their physicochemical, pharmacological, and toxicological properties, using the Liver Toxicity Knowledge Base (LTKB) (Chen et al., 2013b). Our analysis identified specific drug properties associated with an increased reporting frequency of liver events in specific subpopulations classified by gender and/or age (i.e., age-, gender-biased reporting frequency), which could help us better characterize the susceptibility among specific subpopulations and generate hypotheses for future investigations.

2. Methods

2.1. Study design

To explore the potential interplay between drug properties and host factors, i.e. age and gender, in liver events reporting frequency (RF), we performed a data-mining analysis using the WHO VigiBase™ on 375 drugs associated with hepatotoxic potential. We first identified drugs that are associated with age- or gender-biased liver events RF. Then, we characterized drug properties of the identified drugs with age- or gender-biased liver events RF, comparing to those drugs with no age- or gender-bias in liver events RF, for the purpose of hypothesis generation. Detailed methods are described below.

As the study was conducted using only de-identified data, without accessing personally identifiable information, it does not constitute human subjects research and does not require IRB approval, as defined under federal regulations [45 CFR 46.102 (f)].

2.2. Data sources

We used the WHO global individual case safety report database of VigiBase™, issued in the fourth quarter of 2014. The VigiBase™ is the world's largest spontaneous adverse event reporting system, which accumulates more than 8.4 million reports from 104 countries, mainly from North America and Europe, including both regulatory and voluntary sources. This database has been utilized in pharmacovigilance research and big data analysis by regulatory bodies and industry.

To characterize properties of identified drugs, we used the LTKB at National Center for Toxicological Research, which accumulates information on drugs' physiochemical, pharmacological, and toxicological properties as well as their signature patterns of clinical DILI (Chen et al., 2013b). More specifically, the database covers more than 2000 US-marketed prescription drugs and provides a unified data source for drug properties pertaining to hepatotoxicity, including lipophilicity, peak drug concentration (Cmax), half life ($T_{1/2}$), plasma protein binding, reactive metabolites formation, mitochondrial lability, oxidative stress, and inhibition of transporters (i.e. bile salt export pump or BSEP), multidrug-resistance associated protein (MRP 2,3,4), daily recommended dose, and dominant clinical "signature" or injury patterns (hepatocellular vs. cholestatic) (Chen et al., 2013b).

2.3. Primary study drugs

We defined a group of drugs that have established hepatotoxic potential in humans. Two previously published lists of drugs that have evidence-based hepatotoxic potential in humans (Chen et al., 2011; Suzuki et al., 2010) were mapped to drugs populated in the VigiBase™ that were reported with any types of liver events. After excluding combination drugs, herbal medicines, and supplements, we identified 375 drugs with evidence-based human hepatotoxic potential, including 189 'most-DILI concern" (Chen et al., 2011) and 296 drugs from the unified drug list (Suzuki et al., 2010), which were used for this data-mining analysis.

2.4. Liver events

Liver events were defined using the Medical Dictionary for Regulatory Activity (MedDRA). Custom liver event terms for hepatocellular injury, cholestatic injury, acute liver failure, and overall liver events were created combining groups of 'Preferred Terms' (codes from MedDRA) (Suzuki et al., 2015). The overall liver event term (combining hepatocellular injury, cholestatic injury, and acute liver failure event terms) was used to identify drugs with age-, or gender-biased liver events RF.

2.5. Analytic methods

The reporting frequency data were computed using the Empirica™ Signal application (Oracle Corporation, Redwood Shores, CA, USA). A relative reporting ratio (RRR) was defined as the observed count divided by the expected count. Empirical Bayes Geometric Mean of RRR (EBGM) is defined as the exponential value of log (RRR) under the posterior probability distributions for each true RRR. The lower and upper 90% confidence limits (EB05, EB95) for the RRR were derived from the posterior probability distribution (DuMouchel, 1999, 2001).

EBGMs of the 375 study drugs were calculated using the entire reports in the database as well as partitioning the reports into 4 groups by gender and age $<$ or ≥ 50 years. In this analysis, we used the age of 50 years, the average age at menopause in the US (Nichols et al., 2006) as an age cut-off as we were interested in whether the proxy of female menopausal status may influence gender differences in RF. Pediatric cases (age $<$ 18 years) were excluded from this analysis as their physiological and social attributes differ from those of the adult population. The computed age-, gender-specific EBGM and 90% CI were compared among the four age/gender groups to identify drugs with significant differences in gender- and age-specific RF (Fig. 1). Identification criteria for each drug group are summarized in Fig. 1. Among them, drugs with a higher RF in men vs. women, a higher RF in women vs. men, a higher RF in women vs. men (only in age $<$ 50 years), a higher RF in age $<$ 50 years, and a higher RF in age ≥ 50 years were further characterized for their properties while comparing with drugs with no gender-biased reporting and drugs with no age-biased reporting (control groups).

2.6. Characterization of drug properties

After identifying drugs with age-, gender-biased liver events RF, the drugs were reviewed for total numbers of reports (either suspected drugs or co-medications) in the VigiBase™, total numbers of reported liver events in the VigiBase™, and their FDA-approved indications to look for 1) drugs that are rarely reported and 2) drugs that have gender-specific indications. Numbers of gender-, age-specific reports (computed by partitioning all the reports in the database) were also reviewed to look for 3) drugs that are reported with significant age-/gender-differences (i.e., sex-/age-biased reporting). Drug selection process is depicted in Fig. 2. Eighteen drugs were excluded from the analysis due to their low reporting (total numbers of reports $<$ 100 in the database) due to the concern over data reliability. One drug was also excluded due to its low liver event reporting (≤ 5) for the same reason. Further, 15 drugs were excluded due to sex-biased reporting while 7 drugs were excluded due to age-biased reporting (the above