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Age-related differences in reporting of drug-associated liver injury: Data-mining of WHO Safety Report Database

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ABSTRACT

Background/aims: Age-differences in the frequency and manifestations of drug-induced liver injury are not fully characterized. Data-mining analyses were performed to assess the impact of age on liver event reporting frequency with different phenotypes and agents.
Methods: 236 drugs associated with hepatotoxicity were evaluated using the Empirical Bayes Geometric Mean (EBGM) of the relative reporting ratio with 90% confidence interval (EB05 and EB95) calculated for the age groups: 0–17, 18–64, and ⩾ 65 years (or elderly), for overall, serious (acute liver failure), hepatocellular, and cholestatic liver injury, using the WHO Safety Report Database.
Results: Overall, cases of age 0–17, 18–64, and 65 years or older comprised 6%, 62%, and 32% of liver event reports. Acute liver failure and hepatocellular injury were more frequently reported among children compared to adults and the elderly while reports with cholestatic injury were more frequent among the elderly ($p < 0.00001$). A potential to cause mitochondrial dysfunction was more prevalent among the drugs with increased pediatric reporting frequency while high lipophilicity and biliary excretion were more common among the drugs associated with higher reporting frequency in the elderly.
Conclusion: Age-specific phenotypes and potential drug properties associated with age-specific hepatotoxicity were identified in reported liver events; further analyses are warranted.

1. Introduction

In the United States, drug-induced liver injury is the leading cause of death from acute liver failure in adults (Ostapowicz et al., 2002). Older adults (age 60 and over) exhibit generally similar outcomes to younger adults (Schiødt et al., 2009). In contrast, children with drug-induced acute liver failure can exhibit much poorer outcomes than adults, with a 73% one-year mortality after liver transplantation for antiepileptic-induced liver failure (Mindikoglu et al., 2009). Fortunately, children rarely exhibit drug-induced acute liver failure, which accounts for only 20% of acute liver failure events (Murray et al., 2008). While children (<18 years) comprise 26% of the US population, they account for only 7% of reported serious drug adverse events overall (Moore et al., 2007), with hepatic events accounting for only 1% of reported pediatric adverse drug events globally (Ferrajolo et al., 2010).

Overall, serious drug adverse events account for 3–6% of hospital admissions (Moore et al., 2007). The average ambulatory Medicare patient consumes 4 medications or more daily (Gurwitz et al., 2003), and most (63%) use complementary and alternative medications (Cheung et al., 2007), contributing to adverse drug reactions (Gurwitz et al., 2003). While the elderly (⩾65 years) constitute only 13% of the US population (Moore et al., 2007), they account for approximately one third of serious adverse drug reports. The US elderly population is growing rapidly and will double by 2050 (U.S. Census Bureau, 2013), so identifying and addressing risk factors for drug-induced liver injury in this vulnerable population is a key concern.

Abbreviations: DILI, drug-induced liver injury; EBGM, Empirical Bayes Geometric Mean; EB05 and EB95, Empirical Bayes Geometric Mean of the relative reporting ratio with 90% confidence interval; ICSR, individual case safety report; MedDRA, Medical Dictionary for Regulatory Activity; WHO, World Health Organization.

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In addition to age, drug-specific factors affect drug-induced liver injury. For example, most drugs causing drug-induced liver injury are administered at high daily doses of 50 mg or more (Lammert et al., 2010) and undergo significant hepatic metabolism (Lammert et al., 2008). Furthermore, most ($\geqslant$85%) drugs with both a high daily dose ($\geqslant$100 mg) and high lipophilicity (with octanol–water partition coefficient, or $\log P \geqslant 3$) are significantly associated with hepatotoxicity (Chen et al., 2013).

Age and development substantially influence drug metabolism (Kearns et al., 2003; Klotz, 2009), inflammation and regeneration (Hohensinner et al., 2011; Grolleau-Julius et al., 2010; Chen et al., 2010). Children exhibit age-related changes in drug absorption, distribution, metabolism and excretion, which are most marked in infancy and are generally similar to adults in children over age 8 (Kearns et al., 2003). Homozygous mitochondrial DNA polymerase gamma gene (POLG1) polymorphisms frequently manifest in the first few years of life; these vulnerable children are highly susceptible to drug-induced acute liver failure and fatality (Squires et al., 2006; McFarland et al., 2008).

Liver mass, regeneration, and hepatic blood flow decrease with normal aging, resulting in lower first pass clearance of select drugs in the elderly (Klotz, 2009; Schmucker and Sanchez, 2011), although the activity of most Phase I and II enzymes are unaffected by aging (Klotz, 2009; Schmucker and Sanchez, 2011; Hunt and Strater, 1990; Hunt et al., 1992a,b; Schwartz, 2006). However, inter-individual pharmacokinetic variability can increase due to aging-related changes in drug disposition in the elderly with increasing body fat or delayed gastric emptying, decreased renal blood flow and excretion (Klotz, 2009), and decreased mitochondrial function (López-Lluch et al., 2008). A moderate decline in biliary function, with decreased bile flow and bile acid secretion, and in liver regeneration following injury is observed in the elderly (Schmucker and Sanchez, 2011). Aging-related relative immune deficiencies and increased autoimmunity are associated with shortening telomeres, increasing CD28-T cells contributing to auto-reactivity, DNA hypomethylation, and alterations in histone acetylation (Hohensinner et al., 2011; Grolleau-Julius et al., 2010). Due to these aging-related physiologic changes, drugs of high lipophilicity, drugs exhibiting high first pass clearance, or those undergoing biliary excretion or causing autoimmune injury, may more commonly result in hepatotoxicity in the elderly.

To minimize the risk of severe and unpredictable liver injury in vulnerable populations, it's essential to better understand age-specific susceptibility and manifestations of drug-induced liver injury. As drug-induced liver injury occurs infrequently (Sgro et al., 2002; de Abajo et al., 2004), a large database is needed to examine its occurrence and risk factors. The World Health Organization (WHO) Safety Report Database, VigiBase™, is the world's largest individual case safety reporting system, with more than 8.4 million case reports from both regulatory and voluntary sources in 104 countries since 1968 (Lindquist, 2008; Caster et al., 2014). VigiBase™ is broadly utilized to examine drug safety and generate hypotheses on hepatotoxicity risk factors (Ferrajolo et al., 2010; Caster et al., 2014; Suzuki et al., 2010; Petronijevic and Ilic, 2013). To assess the impact of age on liver event reporting frequency and phenotype, two hundred thirty-six drugs associated with hepatotoxicity were evaluated in the WHO Safety Report Database. Drugs associated with a higher reporting frequency by age group were further analyzed by physicochemical properties, daily dose, or other attributes for the purpose of generating hypothesis pertaining to age-specific susceptibility. With inborn mitochondrial genetic defects manifesting early in life (Mindikoglu et al., 2009; Squires et al., 2006; McFarland et al., 2008), we hypothesized that mitochondrial dysfunction might be more common in drugs associated with pediatric hepatotoxicity, and that drugs with high lipophilicity, high first pass clearance, or biliary excretion may be more highly represented in the elderly. If these hypotheses are validated in future research, the identification of aging-related susceptibilities to targeted drug properties could be used to design and select safer new drugs for these age groups.

2. Methods

2.1. Study design

We conducted a data-mining analysis applying a disproportionality analysis to a large global safety database, VigiBase™ to characterize age-differences in reporting frequency of liver events and its clinical phenotypes. As the released VigiBase™ version contains only coded data and no personally identifiable information, this study does not constitute human subjects research and does not require IRB approval, as defined under federal regulations [45 CFR 46.102 (d or f) and 21 CFR 56.102(c)(e)(l)].

2.2. Data source

This analysis was performed with the WHO individual case safety report (ICSR) VigiBase™ data set released in the third quarter of 2012.

2.3. Reporting frequency of liver events

Disproportionality of reporting frequency ratios for a drug-liver event pair in VigiBase™ were determined, relative to all other drugs and events in the database (relative reporting ratio) (Suzuki et al., 2010; Almenoff et al., 2005, 2006). Age-specific estimates were calculated partitioning the database based on the age groups: children (0–17 years), adults (18–64 years), and the elderly (65 years or older). Applying Bayesian statistics, the relative reporting frequency of liver events was converted to the Empirical Bayes Geometric Mean (EBGM) of the relative reporting ratio with a 90% confidence interval (Suzuki et al., 2010) (CI) (EB05 and EB95) using Empirica™ Signal (Oracle Corporation, Redwood Shores, CA) for 3 different age groups. If no age information was available, liver-related cases were excluded. The above method is depicted in Fig. 1a.

EBGM values demonstrate the strength of the association of the drug and the adverse event pair to display the relative reporting rates (Almenoff et al., 2005, 2006). For example, an EBGM > 2 indicates that the drug-adverse event combination is reported at a > 2-fold higher frequency than expected reporting frequency computed assuming that there is no association between the drug and the adverse event. An EBGM $\geqslant$ 2 for a drug-adverse event combination is internationally endorsed as a significantly increased reporting frequency (a positive association between the drug and the adverse event) (Suzuki et al., 2010). The 90% confidence intervals [lower limit (EB05) and upper limit (EB95)] are calculated to assess differences in reporting frequency (Suzuki et al., 2010). To examine reporting differences in the current study, the EB05 and EB95 intervals are compared for an overlap (Suzuki et al., 2010). The identification of drugs associated with age-specific reporting frequency is depicted in Fig. 1b.

To examine the reporting frequency of liver events of different clinical phenotypes, EBGM and 90%CI were computed using 4 custom liver events terms, including acute liver failure and a combined overall liver injury term previously applied in a Vigibase™ analysis (Suzuki et al., 2010). The custom liver event terms for hepatocellular and cholestatic injury were developed by two board-certified hepatologists and two pharmacovigilance experts by combining groups of 'Preferred Terms' (codes from the Medical